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Abstract Book

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Cambridge, UK.

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S Greene
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S5

Other forms of diabetes
Nicola Bridges
London, UK.

Diabetes which is not type 1 or type 2 makes up a very small proportion of all diabetes cases in children and adolescents. The value of recognising these is that treatment and outcome can be very different from that seen in type 1 or 2.
Other forms of diabetes can be divided into several groups:
1. Genetic diabetes including MODY and neonatal diabetes. MODY can be confused with type 1 diabetes in children. Making the diagnosis can be important in determining treatment (some types are better managed on oral medication) and can have genetic consequences for the family.
2. Diabetes associated with syndromes such as Prader Willi, Alstroms, and Laurence Moon Biedl. The diagnosis is usually clear, with a diabetes pattern similar to type 2 diabetes. Management can be complicated by other co-morbidities and learning difficulties.
3. Mutations of the insulin receptor, such as leprechaunism or Rabson-Mendenhall syndrome.
4. Diabetes related to pancreatic failure such as in Cystic Fibrosis and haemochromatosis.
For individuals with other complex medical problems, management of diabetes can be a significant burden. A balance needs to be struck between providing a regimen and treatment goals which are achievable for the patient and giving best diabetes control to maintain health. A good example of this is cystic fibrosis related diabetes where previously diabetes treatment was though to be too burdensome for individuals with such significant other health problems. However, recognition of the impact of diabetes and glucose control on lung function and survival in CF has changed this completely, and individuals with CF are screened for diabetes and insulin treatment started at an early stage.

S6

T2DM
S Ehtisham
Manchester, UK.

Abstract unavailable.

S7

Hyperinsulinaemic hypoglycaemia
Khalid Hussain
Developmental Endocrinology Research Group, Clinical and Molecular Genetics Unit, UCL Institute of Child Health, Great Ormond Street Hospital for Children NHS Trust, London WC1N 3JH, UK.

Hyperinsulinaemic hypoglycaemia (HH) is a cause of severe and persistent hypoglycaemia in the newborn period. It is an extremely heterogeneous disorder with respect to clinical presentation, pancreatic histology and molecular biology. The clinical severity of HH varies mainly with age at onset of hypoglycemia (severe hypoglycemia in neonates) and has major consequences in terms of therapeutic outcome and genetic counseling. The commonest genetic cause of persistent HH are autosomal recessive mutations in the genes *ABCC8* and *KCNJ11* (encoding the two subunits SUR1 and KIR6.2 respectively) of the pancreatic ATP-sensitive potassium channel (K_{ATP}).
Histologically, there are two major subtypes of the disease, namely focal and diffuse. Both the diffuse and focal forms share a similar clinical presentation, but result from different pathophysiological and molecular mechanisms. In addition, diffuse HH usually presents as an autosomal recessive disorder, whereas focal HH is sporadic. Differentiation of diffuse from focal disease is important in terms of management as focal disease requires a limited pancreatectomy (curing the patient) whereas diffuse disease will require a near total pancreatectomy. Imaging with ^{18}F-DOPA-PET/CT is now the gold standard for differentiating diffuse from focal disease. The rapid and accurate diagnosis of HH is very important, as a delay and inappropriate management can lead to brain damage. During the talk I will discuss the clinical presentation and diagnosis of HH. I will outline a management plan and show how advances in molecular biology and radiological imaging techniques have radically changed our approach to these very complex patients.

RCN CYP Diabetes Community Session

S8

A good start does it matter? Intensive diabetes management from diagnosis
Nils Krone
School of Clinical and Experimental Medicine, Centre for Endocrinology, Diabetes and Metabolism, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK.

Paediatric diabetes ranks amongst the commonest chronic diseases in childhood and affects about 23 000 children under 17 years. Acute medical management at manifestation is well established and successfully conducted in the vast majority of cases. The chronic long-term treatment is challenging and involves self-managed, regular subcutaneous insulin administration, together with diet, exercise and lifestyle support to avoid short and long-term complications. Glycaemic control in UK children is worse than in many other European countries. Insulin therapy is the central part of structured treatment and education programs for children with type 1 diabetes. During the initial structured education, patients, parents and other care takers should be enabled to conduct insulin therapy independently. This should include a good mix of theoretical and practical skills, which is required from diagnosis. Fear of parents and health care professionals of hypoglycaemic episodes should be overcome by improving self-management skills and competencies. It is important to communicate that conventional therapy does not allow for physiological insulin replacement. Multiple daily injection strategies are preferred, but they do not necessarily equal an intensified conventional therapy (ICT). ICT aims to mimic physiologic insulin secretion with variable insulin doses including different carbohydrate to insulin ratios at different times, considering different sensitivities and different circadian rhythms according to age in an individualised fashion. An even closer to physiologic replacement can be achieved using continuous subcutaneous insulin infusion via insulin pumps. The more sophisticate the insulin replacement method

becomes the more theoretical and practical knowledge is required by patients, parents and healthcare professionals. In addition, the self-monitoring of blood glucoses and tightly linked improvement of glycaemic control should be communicated from the beginning. Detailed education should start at diagnosis to enable patients and their families to manage their diabetes as early as possible at a high level of independence to improve long-term outcomes.

S9

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Z Mughal
Manchester, UK.

Abstract unavailable.

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Can peer review provide quality assurance and remove the postcode lottery?

R Bridgeman
London, UK.

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S11

Can peer review provide quality assurance and remove the postcode lottery?

F Campbell
Leeds, UK.

Abstract unavailable.

S12

Can technology enhance consultation style

P Adolfson

Abstract unavailable.

S13

Helping children to learn about and understand their illness: a quick look at theory and its application

Alan Pritchard
Warwick Institute of Education, University of Warwick, Coventry, UK.

This short presentation will consider the fact that many adults underestimate children's ability to understand many things – this works in two ways, sometimes children understand more, and sometimes less than we might imagine – and by doing so may cause upset and misunderstanding. In any case we will see that all of us, including children, try to make sense of our surroundings, of new information, and of what happens to us, and children, in particular, need a certain amount of help with this process. A brief outline of constructivist learning theory will provide a foundation for building ideas about how children might come to terms with new and sometimes confusing information about their health. Some examples of misunderstanding will be considered and some practical suggestions for helping children through what can be a very difficult time will be suggested. The presentation will be necessarily brief and should be considered as a small window into rather large topic.

S14

The role of the consultant nurse in paediatric diabetes

R Thompson
London, UK.

Abstract unavailable.

S15

Diabetes self-management education: can it change diabetes outcomes?

Sheridan Waldron

Diabetes self-management education (DSME) in the UK is less well defined in paediatrics than in adults. Moreover, there is no nationally validated programme of education for paediatrics consequently the 70% of services that offer structured education have developed them locally. As we move towards a new system of payment for paediatric diabetes, the Best Practice Tariff, services will need to demonstrate that they supply a structured education programme from diagnosis and throughout on-going care.

The SWEET Project EU (2008–2011) was initiated to improve standards of care across Europe. Comparing and contrasting models of education between countries has highlighted the significance and major contribution that education makes to diabetes outcomes. Countries that have adopted a holistic approach to education through: organised, standardised, validated education for children and young people, (CYP), their families and health care professionals (HCPs) show impressive clinical outcome data. However, studies show that centre differences still exist but strong benefits have been found from: intensive education at diagnosis; standardised age and maturity on-going education; accredited diabetes educators; a multi-disciplinary approach; larger clinic size and maintaining contact with young people. Data also suggests lower glycated haemoglobin improves quality of life in CYP.

Data from the recent National Diabetes Audit shows the glycaemic control of our CYP with diabetes is extremely poor in comparison to some European counterparts. We have no option but to make radical changes to our present models of care and the delivery of Diabetes Self-management education. The UK can benefit from the experiences of countries that have developed a holistic, validated and standardised programme of education for CYP, their families and HCPs.

Symposium 1–Update on Adrenal Disorders

S16

Familial glucocorticoid deficiency: an update

Adrian J L Clark, Claire Hughes, Eirini Meimaridou & Lou Metherell
William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, Centre for Endocrinology, Charterhouse Square, London, UK.

Familial glucocorticoid deficiency (FGD) is a rare autosomal recessive disorder characterized by resistance to the action of ACTH leading to glucocorticoid deficiency with preserved mineralocorticoid and gonadal function. In 1993 we identified mutations in the ACTH receptor (melanocortin 2 receptor; *MC2R*), although these only explained around 25% of cases. More recently a traditional homozygosity mapping approach identified mutations in a novel gene which we named melanocortin 2 receptor accessory protein (*MRAP*). MRAP encodes a small membrane protein essential for trafficking of the MC2R to the cell membrane and for binding of ACTH. We also demonstrated that the FGD phenotype may also be associated with partially inactivating mutations in *STAR*. Despite these findings, around 50% of all cases of FGD have no recognized genetic explanation. Application of homozygosity mapping, targeted exon capture and high throughput sequencing in consanguineous and multiply affected families has recently identified two new genes. These are 1) a gene essential for

DNA replication, which is mutated in a phenotypic variant of FGD found exclusively in the Irish traveler population, and 2) a gene that is essential for maintenance of the mitochondrial redox state. In view of the function of this latter gene other components of the mitochondrial redox pathway were screened and an inactivating mutation in a further gene with a related function was identified in FGD. These discoveries reveal novel mechanisms underlying adrenal failure, although further genetic causes remain to be identified.

S17

Recent advances in our understanding of adrenal development and disease

John Achermann
UCL Institute of Child Health, London, UK.

In humans, the adrenal gland develops from the intermediate mesoderm at around 4 weeks gestation and undergoes a series of distinct morphological and functional changes throughout pre- and post-natal life. Two key transcriptional regulators of adrenal development are the nuclear receptors DAX-1 (*NR0B1*) and steroidogenic factor-1 (SF-1, *NR5A1*, Ad4BP). Mutations or deletions of DAX-1 result in X-linked adrenal hypoplasia congenita (AHC). Boys with this condition typically present with salt-losing adrenal failure in early infancy or throughout childhood and show evidence of hypogonadotropic hypogonadism (HH) and impaired spermatogenesis in adolescence. DAX-1 mutations are a relatively frequent cause of adrenal hypoplasia in males, especially with a family history of X-linked adrenal failure or when HH is present. Alternative presentations of X-linked AHC include isolated mineralocorticoid insufficiency, premature sexual maturation, adrenal hypoplasia in girls with skewed X-inactivation and adult-onset adrenal failure/HH. Despite this clinical insight, the molecular aetiology of X-linked AHC remains poorly understood. The related nuclear receptor SF-1 regulates transcription of many key target genes involved in adrenal development and function. Partial loss of SF-1 function more frequently results in 46,XY DSD or primary ovarian insufficiency, but in most cases adrenal reserve is normal. Syndromic causes of adrenal hypoplasia include changes in sonic hedgehog (SHH), WNT4 (causing SERKAL syndrome), and IMAGe syndrome (IUGR, skeletal anomalies, adrenal hypoplasia and mild genital features). Pbx1 and Cited2 are implicated in adrenal development in mice, but no significant changes in these factors have been found in humans with adrenal hypoplasia. The search continues, therefore, for new transcriptional regulators and networks that account for adrenal hypoplasia where the cause is currently unknown.

S18

Health problems in congenital adrenal hyperplasia: a UK perspective

Nils Krone
School of Clinical and Experimental Medicine, Centre for Endocrinology, Diabetes and Metabolism, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK.

Congenital adrenal hyperplasia represents a group of autosomal recessive disorders in steroidogenesis causing deficient cortisol biosynthesis. Following the introduction of life-saving glucocorticoid replacement 60 years ago, congenital adrenal hyperplasia (CAH) has evolved from being perceived as a paediatric disorder to being recognized as a lifelong, chronic condition affecting patients of all age groups. Increasing evidence suggests that patients with CAH have an increased risk to develop health problems during adult life, with signs and symptoms of forerunner conditions of adult disease already emerging during the time of paediatric care. Recent data from a prospective cross-sectional study of adults with CAH attending specialized endocrine centres across the United Kingdom suggested an impaired health status of adults with CAH. Glucocorticoid replacement was generally nonphysiological, and androgen levels were poorly controlled. As reported in other outcome studies CAH patients were significantly shorter and had a higher body mass index. Blood pressure was not grossly altered. Only women with classic CAH had increased diastolic blood pressure. However metabolic abnormalities were common, including obesity (41%), hypercholesterolaemia (46%), insulin resistance (29%), osteopaenia (40%), and osteoporosis (7%). Overall fertility was compromised and subjective health status was significantly impaired. A very good genotype-phenotype correlation is well established in early life. However, the severity of genetic alteration did not correlate with the outcome in adult CAH patients. Currently, a minority of adult United Kingdom CAH patients appear to be under endocrine specialist care. Improvements in the clinical management of adults with CAH are required. Comprehensive data on the general health status during childhood and adolescence do not exists. These are warranted to identify the onset of co-morbidities and develop paediatric preventive health care provision strategies in CAH to improve primary and secondary prevention of long-term health problems.

Symposium 2–Pubertal Disorders

S19

Novel insights into hypogonadotrophic hypogonadism

N Pitteloud

Abstract unavailable.

S20

Clinical management of late puberty

Leo Dunkel
William Harvey Research Institute, Barts and the London, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ, UK.

Constitutional delay of growth and puberty (CDGP) is the most common diagnosis among males and females with pubertal delay, but it can be diagnosed only after exclusion of other underlying conditions. Most of the boys with delayed puberty have CDGP, but about 5–10% have hypergonadotropic hypogonadism (including Klinefelter), 10% have permanent hypogonadotropic hypogonadism (including Kallmann syndrome and idiopathic hypogonadotropic hypogonadism), and 10% have a transient form of hypogonadotropic hypogonadism (delayed maturation of the HPG axis secondary to underlying conditions, e.g. inflammatory bowel disease).

Evaluation

First, exclude underlying disorders. Eventual normal progression of puberty verifies diagnosis of CDGP, whereas absent, slow or cessation of development is consistent with permanent hypogonadism. A complete family history is important, because CDGP clusters in families. Delayed puberty in a parent or sibling followed by spontaneous onset of puberty suggests CDGP. Bilateral cryptorchidism and/or small penis at birth, hyposmia, or anosmia suggest hypogonadotropic hypogonadism.

Previous height and weight measurements are also critical. Delayed puberty is often associated with short stature and slow growth for age, although height and growth velocity are usually appropriate for bone age. Individuals who are underweight for height have a higher likelihood of an underlying condition delaying HPG axis activation. Conversely, in boys, unlike girls, overweight is associated with later pubertal development. In boys, Tanner stage 2 genitalia and testicular volume of >3 cc indicates initiation of central puberty. Delayed bone age is not diagnostic of CDGP and is seen also in chronic illnesses, hypogonadotropic hypogonadism and gonadal failure. However, adult height prediction may be an important part of counselling if short stature is an issue.

Basal LH and FSH levels are low both in CDGP and hypogonadotropic hypogonadism. Conversely, in gonadal failure, basal levels are usually elevated. Patients with hypothalamic-pituitary tumours causing gonadotropin deficiency may have additional pituitary hormone deficiencies. After initial evaluation most patients with delayed puberty will have the likely diagnosis of CDGP. If basal gonadotropin levels are inconclusive, stimulation by GnRH may be helpful. Pubertal LH levels indicate reactivation of the HPG axis, and secondary sexual development is likely to occur within 1 year. However, the GnRH test alone often cannot differentiate CDGP from IHH because prepubertal values may be observed in IHH or in individuals with CDGP who have not yet activated the HPG axis. IHH can be diagnosed if endogenous puberty has not begun by age 18 years. Growth hormone secretion in the basal state, as well as after provocation testing, may be decreased in CDGP. If concerns about growth are sufficient enough to warrant growth hormone provocation testing, sex steroid priming is necessary for reliable results in patients with delayed puberty. A patient with a normal height velocity and a plasma IGF1 level above the mean for age does not require provocation testing.

In CDGP the options are observation or low dose testosterone or estrogen therapy in boys and girls, respectively. Therapy is usually initiated to assuage psychosocial concerns that may derive from difficulties with peers, decreased self-esteem, and anxiety about growth rate and/or body habitus. However, therapy is usually not initiated solely for medical reasons, such as accrual of bone mass. Sex steroid treatment leads to increased growth velocity and sexual maturation and positively affects psychosocial well-being without significant side effects,

rapid advancement of bone age or reduced adult height. For a subset of patients with CDGP, short stature is as or more concerning than delayed puberty. Indeed, in various reports CDGP is considered a subgroup of idiopathic short stature and patient with CDGP do have low GH responses during provocation testing unless they are primed with sex steroids. GH treatment has a modest if any effect on adult height in adolescents with CDGP, and its routine use in CDGP is not recommended.
In patients with CDGP and short stature, an additional therapeutic approach is aromatase inhibition. Estrogen is the predominant hormone needed for epiphyseal closure, and therefore AIs could prolong linear growth and potentially increase adult height. However, characteristics of patients who respond and those who do not as well as the optimal timing, dose, and duration of AI treatment remain unresolved. The full side effect profile has also not been established. Thus, the use of aromatase inhibitors, even in adolescents with compromised predicted adult height, should be considered experimental.

Symposium 3–Insulin Resistance and Type 2 Diabetes: Novel Insights

S21

Genetic disorders of insulin signalling
Robert K Semple
University of Cambridge Metabolic Research Laboratories, Cambridge, UK.

Driven by the rising global tide of obesity, insulin resistance is already at pandemic levels, and is intimately associated with major pathologies including type 2 diabetes, ovulatory dysfunction and hyperandrogenism, the spectrum of fatty liver disease, and disorders of growth including cancer. Yet despite intensive study of prevalent forms of the condition, major questions remain both about the nature of the genetic predisposition to insulin resistance, and the mechanisms linking it to clinical disease. To circumvent the problem of discerning causation in associated clinical phenomena, we have adopted the strategy of seeking novel insulin signalling defects in rare and extreme disorders of insulin action, and have recently made a series of new discoveries of genetic abnormalities in insulin signalling using exome-wide sequencing. I shall review current knowledge of primary insulin signalling disorders, concentrating on novel disorders of growth, insulin resistance and hypoglycaemia, and illustrate the insights into prevalent pathophysiology to be gained from these rare conditions.

S22

Early intervention in type 2 diabetes mellitus
Rury Holman
Diabetes Trials Unit, OCDEM, University of Oxford, Oxford, UK.

The number of people worldwide with diabetes is predicted to exceed 370 million by the year 2030. Over 90% of these will have type 2 diabetes with a twofold greater risk of heart disease and stroke than in the general population, and a reduction in life expectancy of five or more years.
Type 2 diabetes is a condition of relative insulin deficiency. Insulin secretory responses to meal challenges are delayed and prolonged and, although fasting insulin levels may be normal or elevated, they are insufficient to meet the metabolic demand or overcome the decreased insulin sensitivity which develops in many patients prior to diagnosis. Insulin is the oldest medication available for the treatment of diabetes and in many ways is a logical choice, providing hormone replacement therapy for an endocrine deficiency disease.
First-line therapy with a basal insulin in UKPDS was associated with a reduced risk of diabetic complications, with only modest weight gain ($\sim$2.5 kg over 10 years) and low levels of hypoglycaemia ($\sim$5% of patients per year). Early addition of basal insulin in UKPDS patients with fasting plasma glucose levels $>$6.0 mmol/l on maximum sulfonylurea therapy resulted in more of them achieving HbA1c levels $<$7.0% ($<$53 mmol/mol), with no greater weight gain and fewer hypoglycaemic episodes.
The recent treating to target in type 2 diabetes (4-T) trial confirmed that early addition of a basal insulin, in patients with inadequate glycaemic control on maximum metformin and sulfonylurea therapy, achieved similar or lower HbA1c values than adding biphasic or prandial insulin, and with less hypoglycaemia or weight gain. The ADA/EASD consensus algorithm for the management of hyperglycaemia in type 2 diabetes continue to recommend the addition of basal insulin to metformin therapy, or to metformin plus sulfonylurea therapy, whenever glycaemic targets are not met.

Plenary Guest Lecture

S23

Advances in our understanding of the genetic causes of obesity
Ismaa Sadaf Farooqi
University of Cambridge, Cambridge, UK.

Whilst the recent rise in the prevalence of childhood obesity has been driven by environmental factors, there is considerable evidence from twin and adoption studies that body weight and fat mass are highly heritable traits and differences in susceptibility to obesity have strong genetic determinants. The identification of patients with mutations in the gene encoding the hormone leptin, and their successful treatment with recombinant human leptin, have provided insights into the role of leptin responsive pathways in the regulation of eating behaviour, intermediary metabolism, the onset of puberty and T-cell mediated immunity. Leptin acts by regulating a complex network of brain responses that can be studied using functional imaging, to co-ordinate changes in nutritional state with changes in food intake and the 'liking' of food. A downstream target of leptin action, the melanocortin 4 receptor (MC4R), plays a key role in modulating sympathetic nervous system mediated changes in blood pressure. Genome wide approaches including whole exome sequencing are proving to be an increasingly important tool in understanding the genetic heterogeneity associated with common obesity. The discovery of how genetic variation at an individual and at a population level contributes to weight gain will drive further understanding of the pathways involved in energy homeostasis and the potential for new therapeutic strategies.

Symposium 4–Novel therapies/management in Diabetes Mellitus

S24

Islet cell transplantation: an update
Peter M Jones
King's College London, London, UK.

In type 1 diabetes mellitus the insulin-secreting β-cells in pancreatic islets of Langerhans are selectively destroyed by autoimmune assault. Since diabetes is caused by the loss of a single cell type it is amenable to treatment by cell replacement therapy. Advances in islet transplantation procedures have demonstrated that people with type 1 diabetes can be cured by human islet transplantation, but the severely limited availability of donor islets has restricted the wide-spread application of this approach, and driven the search for substitute transplant tissues. Recent experimental studies suggest that three separate sources of tissue show therapeutic potential – xenografts from other species, tissue stem cells and embryonic stem cells. Of these, xenografts are closest to clinical application but there are still major obstacles to be overcome including the development of effective encapsulation strategies to hide the graft from the host's immune system. Insulin-expressing cells have been derived from a number of different stem cell populations but embryonic stem cells and induced pluripotent stem cells offer the major advantage of being able, in principle, of providing the vast numbers of cells required for transplantation therapy. Despite recent experimental advances in generating insulin-expressing cells from stem cells there remain considerable technical problems in generating safe and clinically useful β-cell substitutes.

S25

Immunology and type 1 diabetes mellitus
Mark Peakman
London, UK.

Type 1 diabetes (T1D) is part of a group of disorders termed 'organ-specific autoimmune diseases', involving destructive inflammation focused on the

insulin-producing beta cells in the islet of Langerhans. Patients (frequently children) lose endogenous insulin production and are required to inject insulin several times per day for the remainder of their lives, and, after many years, frequently develop severe life-threatening complications affecting the kidneys, heart and eyes. Beta cell destruction is mediated by T lymphocytes. Our work has focused on identification of the key epitopes of beta cell autoantigens that T lymphocytes recognize during the development of T1D. We have characterized autoreactive CD4 T cells that produce the pro-inflammatory cytokines IFN-gamma and IL17 as well as others that make IL10; these have potent immune regulatory properties and are present in a subset of patients who have delayed diabetes onset. More recently, we have extended our analysis of the epitope repertoire in T1D to include peptides presented by disease-associated MHC class I molecules to CD8 T cells. We have identified novel epitopes in preproinsulin that are processed by an unconventional route and are targeted by cytotoxic T lymphocytes (CTLs) in a high proportion of T1D patients. Finally, we have used knowledge about epitopes to explore the potential for antigen-specific immune modulation in T1D, completing a first-in-man study of proinsulin peptide immunotherapy in patients in order to generate data on safety and biomarkers, and lay the groundwork for future intervention studies designed to examine efficacy.

S26

Update on closed loop systems for the treatment of type 1 diabetes mellitus

Roman Hovorka
University of Cambridge, Cambridge, UK.

Devices for continuous glucose monitoring (CGM) measure interstitial glucose as a marker of changes in blood glucose. Although still lacking the accuracy of blood glucose meters, the CGM devices currently available have improved glucose control. The established technique of continuous subcutaneous insulin infusion (CSII) uses a portable electromechanical pump to mimic non-diabetic insulin delivery, infusing insulin at pre-selected rates. Essentially, a slow basal rate is achieved throughout 24 h, with subject-activated boosts at mealtimes.

CGM devices and insulin pumps can be combined to form closed loop systems. Insulin is then delivered according to real-time glucose sensor data, as directed by a control algorithm, rather than at pre-programmed rates. Only a few closed loop system prototypes have been tested clinically, and progress has been hindered by the suboptimal accuracy and reliability of CGM devices, the relatively slow absorption of subcutaneously administered 'rapid' acting insulin analogues, and the lack of adequate control algorithms. We believe that these problems can be overcome with commercially available CGM and pump delivery systems in combination with advanced control algorithms, such as those based on the model predictive control.

Fully closed loop systems may require ultra-fast insulin analogues, dual hormone approaches or novel methods to accelerate insulin absorption such as dermal delivery. Clinical infrastructure to support the use of closed loop systems will build on existing support for continuous glucose monitors and insulin pumps. This includes the training of healthcare professionals and users, and the establishment of reimbursement strategies together with health economics assessments. Larger outcome trials involving closed loop systems are required in the future.

Endocrine Nurse Session

S27

Brief overview of pituitary tumours

L Martin
London, UK.

Abstract unavailable.

S28

Craniopharyngioma from a surgeon's perspective

C Chandler

Abstract unavailable.

S29

Pre and post op care neurosurgical surgeon's perspective

S Wallington
London, UK.

Abstract unavailable.

S30

Craniopharyngioma from a patient's perspective

H Louise Smith

Abstract unavailable.

S31

Hows, whys and wherefores of Endocrine Testing Part 1

J Kirk
Birmingham, UK.

Abstract unavailable.

S32

Hows, whys and wherefores of Endocrine Testing Part 2

G Butler
London, UK.

Abstract unavailable.

S33

Hows, whys and wherefores o endocrine testing: nurse perspective

K Davies
Clinical Nurse Specialist in Paediatric Endocrinology, Kings College Hospital NHS Trust, London, UK.

It will focus on nursing issues relevant in today's practice, by predominantly centering on the 'Endocrine Testing' section of the competency framework, by exploring the Competent, Experienced and Senior / Expert Practitioner roles with reference to how to carry out dynamic endocrine function tests. Other topics will also be touched upon in order to initiate a discussion amongst all the nurses present, such as consent, information leaflets and other practicalities.

Oral Communications

Oral Communications 1

OC1.1

Surgical treatment of children with hyperparathyroidism: single centre experience

Swethan Alagaratnam[1], Caroline Brain[2], Helen Spoudeas[2], Mehul Dattani[2], Peter Hindmarsh[2], Jeremy Allgrove[3], William Van't Hoff[4] & Tomasz Kurzawinski[1]
[1]Centre of Endocrine Surgery, Great Ormond Street Hospitals NHS Trust/University College London Hospital NHS Trust/Royal Free Hospital NHS Trust, London, UK; [2]Department of Endocrinology, UCL Institute of Child Health, London: Great Ormond Street Hospital for Children and University College London Hospital, London, UK; [3]Department of Paediatric Endocrinology, Barts and the London NHS Trust, London, UK; [4]Department of Nephrology, Institute of Child Health, Great Ormond Street Hospital, London, UK.

Introduction
Hyperparathyroidism (HPT) in children is rare with limited outcome measures post surgery.
Methods
Retrospective case review of 26 (14M) children (<16 years) who underwent parathyroidectomies (PTx) between 1978 and 2011.
Results
Twenty-six children (14M, 12F) included six neonates with neonatal severe HPT (NSHPT) and 20 older children with HPT (13 sporadic, 7 familial).
All NSHPT neonates were symptomatic at presentation with raised serum calcium (3.03–8.10 mmol/l) and parathyroid hormone (PTH) (15.8–360 pmol/l). 90% of older children were symptomatic with raised serum calcium (2.83–4.09 mmol/l) and PTH (9.4–62 pmol/l). Four neonates were tested for mutations of the CaSR gene. Two neonates were second degree relatives and both were identified to be homozygous for Q164X mutation. One neonate was found to have a compound heterozygous mutation with a R680C mutation (paternal) and C60F mutation (maternal). The remaining neonate was identified to have a C570 mutation.
Localisation studies in NSHPT (ultrasound (US), MIBI 2) showed no enlarged glands. In older children sensitivity and specificity of US (13) and MIBI (11) in distinguishing solitary from multi-gland disease was 100%. Accuracy of US and MIBI in predicting laterality of solitary enlarged glands was 100%, and for upper/lower localisation were 72 and 78% respectively.
Children with NSHPT underwent five curative total PTx and one non-curative subtotal PTx. In the older group, children with familial HPT underwent three total and four subtotal PTx (one reoperation in MEN1). Children with sporadic HPT underwent subtotal PTx (before 1980), bilateral neck explorations (1980–2002) and minimally invasive PTx (>2002). All were cured by first operation. Histology in sporadic HPT included 1 multigland hyperplasia and 12 solitary adenomas. None of the children had post operative complications.
Conclusion
Parathyroid surgery in children is safe and minimally invasive PTx is the operation of choice for children with sporadic HPT.

OC1.2

Isolation and characterisation of tumorigenic progenitors/stem cells with a stabilizing mutation in β-catenin, in a mouse model of human adamantinomatous craniopharyngioma

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Somatic stem cells of multiple tissues such as brain, blood, gut epithelium and epidermis, have specific roles in tissue homeostasis and plasticity of cell types. There is evidence that when mutated, such cells, termed cancer stem cells (CSCs) also underlie tumorigenesis, but their presence in many tumours is elusive. In the pituitary gland, somatic stem cells (PSCs) have been previously identified and characterised but little is known about their role in tumorigenesis. Adamantinomatous craniopharyngioma (ACP) is the most common paediatric non-neuroepithelial intracerebral tumour, of hitherto unknown cellular origin. ACP has a highly infiltrative nature, often leading to unacceptably high morbidity and mortality following surgical resection as well as high tendency to recur. We recently generated the first genetic mouse model for ACP by conditional expression of a stable form of β-catenin in the pituitary gland, leading to an activation of the Wnt pathway ($Hesx1^{Cre/+}$;$Ctnnb1^{lox(ex3)/+}$). Unexpectedly, Wnt signalling activation occurs only in a subset of cells. Phenotypic analyses reveal that these cells are quiescent *in vivo*, are undifferentiated and express SOX2 but not SOX9, all of which are features of the PSC population. Combining *in vitro* stem cell culture and time-lapse microscopy, we demonstrate that there is both an expansion of the PSC population and an increase in their proliferation rate, both of which may contribute to formation of the tumour in the ACP model. Moreover, through isolation of these putative β-catenin accumulating CSCs by flow-sorting, we show that they have functional properties of PSCs. Microarray analysis of these cells has revealed a unique genetic signature, with significant elevation of pathways involved in cancer. We present novel data demonstrating that in human ACP, these pathways are also affected and identify these as important targets for future treatments.

OC1.3

High likelihood of malignancy in patients presenting with a thyroid nodule

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Introduction
Thyroid nodules in children are more often malignant than in adult practice (~26 vs 5–10%) and in our locality the incidence of thyroid cancer in young people is increasing. We therefore assessed the presentation, investigation, histology and management of paediatric patients presenting with thyroid nodules.
Methods
This was a retrospective audit conducted at a regional unit (catchment population ~3 million) where young people are likely to be referred. Data were collected for the preceding 15 years with subjects excluded if they were >18 years old, if they were positive for thyroid autoantibodies or if they had a family history of MEN/RET. Patients were identified through endocrine and multi-disciplinary team records and radiology data (neck ultrasound examinations). A nodule was defined as a mass on examination or ultrasound that was ≥1.0 cm in diameter.
Results
Twenty-nine patients were eligible for inclusion. Twenty-seven patients were euthyroid, while the biochemical status of two patients was unknown. All patients underwent a thyroid ultrasound scan except one who underwent neck exploration without imaging. Needle biopsy ($n=25$) disclosed benign lesions in 8 (32%) cases, malignant lesions in 4 (16%) and was inconclusive in 13 (52%) cases. Subsequent histological examination of nodular tissue ($n=23$) disclosed 11 (48%) malignant and 12 (52%) benign lesions. Malignant lesions included papillary and follicular carcinomas, while benign lesions included multinodular goitre and adenomas. Of patients presenting with a palpable thyroid nodule, 38% had malignant disease. No patient with more than one nodule clinically had malignant disease ($P=0.014$).
Conclusion
More than a third of children in our locality with a thyroid nodule and who are thyroid antibody negative will have malignant disease. These figures are greater than most in the literature and patients should be counselled and managed with these figures in mind.

OC1.4

Growth retardation and severe constipation due to the first human, dominant negative thyroid hormone receptor α mutation

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Introduction
Thyroid hormones act via receptors encoded by different genes (*THRA* and *THRB*) generating receptor subtypes (TRα1, TRβ1, TRβ2) with differing, tissue-specific

expression. Resistance to thyroid hormone due to *THRB* defects is well recognised, but no *THRA* mutations have yet been reported. We describe the first case of human TRα-mediated thyroid hormone resistance due to a dominant negative *THRA* mutation.

Results

A 6-year-old female presented with lower segmental growth retardation (height <10th centile), skeletal dysplasia (delayed bone age, femoral epiphyseal dysgenesis, delayed fusion of cranial sutures) and severe constipation. Thyroid function tests showed low/low-normal free T_4 (fT_4), high/high-normal free T_3 (fT_3), low reverse T_3 (rT_3) and normal TSH resulting in a markedly subnormal fT_4/fT_3 ratio. Heart rate, blood pressure (BP) and basal metabolic rate (BMR) were subnormal, but serum sex hormone binding globulin concentrations (SHBG), a hepatic marker of thyroid hormone action, were elevated.

Whole exome sequencing identified a heterozygous nonsense mutation (E403X) in *THRA*, generating a carboxyterminally truncated receptor protein which binds corepressors aberrantly and inhibits wild type receptor action in a dominant-negative manner. Thyroxine treatment suppressed TSH and normalised BMR with a further rise in SHBG; but heart rate, BP, growth and intestinal function remained abnormal.

Conclusion

This patient exhibits tissue-specific hypothyroidism paradoxically associated with only borderline abnormal thyroid hormone levels, synonymous with findings in TRα mutant mice. Some parameters (TSH, SHBG) responded to thyroxine treatment, but cardiac, gastrointestinal and skeletal tissues remained refractory. Such differential tissue sensitivity to thyroid hormone action, reflects preserved hormone responsiveness in TRβ-expressing tissues (e.g. hypothalamus, pituitary and liver) but resistance in TRα-expressing tissues (skeleton, gastrointestinal tract and myocardium). Recognition of hypothyroid features, but associated with a distinctive biochemical profile (low-normal fT_4, high-normal fT_3, low rT_3), may enable future identification of additional cases.

OC1.5

Deconvolution analysis of 24 h serum cortisol profiles informs the amount and distribution of hydrocortsione replacement therapy

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Introduction

Glucocorticoid replacement therapy uses twice or thrice daily regimens of hydrocortisone (HC) with variable distribution of the dose over the day. Deconvolution analysis determines the mass of hormone that needs to be secreted to attain a particular serum concentration. We have used this methodology to determine the amount and distribution of cortisol over a 24 h period.

Methods

Seventy-nine adults (41M) aged 60–74 years and 30 children (24M) aged 5–9 years underwent 24 h serum cortisol profiles with samples drawn at 20 min intervals. Profiles were subjected to deconvolution analysis using a cortisol half-life of 80 min to yield the amount of cortisol released by the adrenal to generate the corresponding serum concentration.

Results

Cortisol secretion occurred in discrete bursts. Daily cortisol secretion was 8.3 (range 5.6–12.4) mg/m^2 per day in adults and 10.6 (range 7.2–16.5) mg/m^2 per day in children. Peak secretion was lower in adults than children ($P<0.001$) but nadir values were similar. Peak secretion occurred at 0720 h in both groups but the nadir was earlier in children (2245 h) compared to adults (2400 h). In adults the distribution of total cortisol over the 24 h period was 08.00–14.00 36%, 14.00–20.00 18%, 20.00–24.00 10%, 24.00–08.00 36% whereas the respective values in children were 27, 21, 7, 45%.

Conclusion

These observations suggest an optimal dosing and distribution regimen for HC replacement. The study raises the question whether a trial of thrice versus four times per day HC therapy should be considered.

OC1.6

Twenty novel mutations in nicotinamide nucleotide transhydrogenase (NNT) causing FGD

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Familial glucocorticoid deficiency (FGD;OMIM 202200) results from the inability of the adrenal cortex to produce cortisol in response to ACTH stimulation. Half of all cases are caused by mutations in *MC2R*, *MRAP* or *STAR*. SNP array genotyping of FGD patients of unknown aetiology mapped a disease locus to chromosome 5p13-q12. Targeted exome sequencing of 5p13-q12 in one patient identified a homozygous mutation, p.Ala533Val, in nicotinamide nucleotide transhydrogenase (NNT), a protein involved in antioxidant defence. Conventional sequencing of 100 FGD patients identified 20 further homozygous or compound heterozygous mutations in 14 other families.

C57BL6/J mice (a natural *nnt* mutant) had slightly hyperplastic, disorganized zonae fasciculata with higher levels of apoptosis than wild-type mice. These mutant mice also had lower basal and stimulated levels of corticosterone than their wild-type counterparts. Knockdown of *NNT* by shRNA in H295R cells increased reactive oxygen species (ROS) and reduced cortisol production. RT-PCR of a tissue panel revealed *NNT* is highly expressed in the human adrenal. *NNT* encodes an integral protein of the inner mitochondrial membrane. Under most physiological conditions, this enzyme uses energy from the mitochondrial proton gradient to produce high concentrations of NADPH. The resulting NADPH is used for biosynthesis and in ROS detoxification by enzymes such as glutathione peroxidases. Previous studies have shown that ROS-mediated disruption of Leydig cell mitochondria inhibits STAR function and Leydig cell steroidogenesis.

Cellular defences against ROS such as O_2^- and H_2O_2 are highly developed and species have evolved several overlapping pathways to deal with it. Taken together our findings that NNT is highly expressed in the adrenal, that its knockdown/out leads to increased ROS and that mutations in the gene result in FGD suggest that NNT is a critical enzyme for ROS detoxification in adrenocortical cells, with its loss leading to defective oxidative stress responses, an impairment of steroidogenesis and hence adrenal insensitivity to ACTH.

OC1.7

Mild GH deficiency due to two novel homozygous mutations in the gene encoding GHRH receptor (*GHRHR*) in a single family

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Introduction

Release of GH by the somatotroph cells of the anterior pituitary is stimulated by GHRH. GHRH acts via its transmembrane receptor, GHRHR, a G-protein coupled receptor that stimulates protein kinase A. Recessive mutations in *GHRHR* are associated with severe isolated GH deficiency (IGHD) with a final height in untreated patients between 130 ± 10 cm (−7.2 ± 1.6 SDS) and 114 ± 0.7 cm (−8.3 ± 0.1 SDS) in males and females respectively.

Objective

We hypothesised that a consanguineous Pakistani family with IGHD in three siblings (two males, one female) would have mutations in *GH1* or *GHRHR*.

Methods

PCR amplification and direct sequencing analysis were used to screen both genes.

Results

In all three siblings we identified two novel homozygous missense mutations (c.11G>A (p.R4Q), c.236C>T (p.P79L)) absent from 200 Pakistani controls, in a conserved region of the extracellular domain of *GHRHR*, predicted to affect protein folding. The brothers were diagnosed with GHD at the age of 9.8 and 6.0 years with a height SDS of −2.24 and −1.23 respectively. Their peak GH to glucagon stimulation was 2.9 μg/l with low IGF1 and IGFBP3. Their sister first presented at the age of 16 years with untreated GHD (peak GH <0.1 μg/l, IGF1<3.3 mmol/l). She had classic GHD with abdominal fat deposition, a high pitched voice, frontal bossing and had a small anterior pituitary on MRI. Surprisingly, she attained an untreated final height of 144 cm (−3.0 SDS), which is the tallest untreated height reported to date. Their mother was compound heterozygous for both mutations; paternal DNA is currently unavailable. Screening of *GH1* revealed no mutation.

Conclusion
We report for the first time to our knowledge the presence of two novel homozygous mutations in *GHRHR*. Contrary to previous reports the phenotype in this family appears to be relatively mild, despite the presence of the two mutations in the same gene.

OC1.8

Mutations in *PROKR2* but not *PROK2* are associated with congenital hypopituitarism and septo-optic dysplasia

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Introduction
Loss-of-function mutations in *PROK2* and *PROKR2* in humans have been associated with Kallmann syndrome (KS), characterised by the combination of hypogonadotrophic hypogonadism with anosmia, suggesting that both are critical for GnRH neuronal development.
Objective
KS has overlapping phenotypes and genotypes through *FGF8* and *FGFR1* with congenital hypopituitarism including septo-optic dysplasia (SOD) and thus we aimed to screen a cohort of such patients ($n=421$) for mutations in *PROK2* and *PROKR2*.
Methods
Patients were screened by direct sequencing analysis with the function of any novel variants tested by intracellular Ca^{2+} mobilisation and stimulation of phospho-inositol turnover.
Results
No mutations in *PROK2* were detected but eight patients with SOD tested positive for heterozygous *PROKR2* variations; p.L173R ($n=4$), p.R268C ($n=2$), p.A51T and p.G371R ($n=1$ each). The former two mutations were previously described as functionally significant; p.A51T is a probable polymorphism. p.G371R is a novel sequence variant at a highly conserved residue and was absent in 480 controls; no functional compromise has been identified to date. A further patient with SOD was homozygous for p.R268C, and a tenth patient with combined pituitary hormone deficiency presented with the functionally significant p.R85L mutation in heterozygosity. Patients presented with hormone phenotypes ranging from isolated GHD to panhypopituitarism including diabetes insipidus. Other features included gastrointestinal dysmotility ($n=1$), schizencephaly ($n=1$) and seizures ($n=2$). Conversely, the unaffected, healthy mother of one of our SOD patients heterozygous for the functionally significant p.L173R, was homozygous for the same change. This implies a digenicity/oligogenicity in the aetiology of SOD, and may suggest the presence of genetic modifiers which are protective. Our data reveal apparent similarities in heterozygous and homozygous phenotypes across the PROKR2 protein with variability in penetrance, and raise questions about the accepted role of *PROKR2* in KS.
Conclusion
PROKR2 appears to be more frequently implicated in SOD than any of the previously described genes, and may reflect an overlap between KS and SOD; however further work is required to fully understand the role of *PROKR2* in these disorders.

Oral Communications 2

OC2.1

Sperm cryopreservation in adolescent minors with cancer: factors predicting pre-treatment semen quality in 79 minors aged 12–18 years over 10 years

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Background
Increased childhood cancer survival has resulted in an accruing cohort faced with potential infertility. We have previously shown that sperm cryopreservation is acceptable to 70–80% of adolescents and testicular volume, LH and testosterone concentrations positively predict success in ~33% that bank. However, little is known about semen characteristics in relation to age and puberty. Here, we present data on our subcohort of 79 boys who produced a semen sample for potential banking before any cancer therapy.
Aims and methods
To determine the relationship between age, Tanner stage, endocrine biochemistry, gonadotoxicity risk and four semen characteristics (sperm concentration/ count/ motility and semen volume) in 79 of 222 adolescent cancer patients aged 12–18 years (median 15.7) over a 10-year period by subcohort analysis.
Results
Higher age and plasma LH increased sperm concentration (age $\rho=0.264$, $P=0.019$; LH $\rho=0.32$, $P=0.025$), sperm count (age $\rho=0.387$, $P=0.000$; LH $\rho=0.355$, $P=0.012$) and particularly semen volume (age $\rho=0.562$, $P=0.000$; LH $\rho=0.333$, $P=0.019$), whilst testosterone only weakly correlated with sperm count ($\rho=0.298$, $P=0.037$). Semen volume was also strongly predicted by Tanner stage ($\rho=0.5$, $P=0.035$) and testicular volume ($\rho=0.748$, $P=0.002$). 20.2% ($n=16$) met WHO criteria for normal adult semen; these tending to be older ($P=0.027$) with higher FSH values ($P=0.048$). After age and gonadotoxicity risk-adjustment, only FSH independently predicted sperm concentration ($P=0.002$), sperm count ($P=0.000$) and the chance of having normal adult semen on all four parameters (OR 1.249, $P=0.022$). Notably all four patients with supraphysiological plasma FSH banked normal adult semen.
Conclusion
To our knowledge this large adolescent dataset is the first report of increasing semen volume with pubertal development as well as age (in health or disease). Whilst increased virilisation (testicular volume, LH, testosterone) is predictive of banking viable sperm, FSH determines semen quality with supraphysiological values not precluding banking or normal semen parameters in adolescent boys.

OC2.2

The assessment of bone microarchitecture by high resolution magnetic resonance imaging (micro MRI) in young adults with childhood onset disease

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Introduction
Dual energy X-ray absorptiometry (DXA) scans are regarded as the gold standard for assessing bone health. However, an inability to distinguish between cortical and trabecular bone as well as the use of inappropriate size corrections mean that this technique is of limited clinical use in conditions affecting either bone microarchitecture or patient size. We have trialled the use of high resolution MRI (micro MRI) in the measurement of bone microarchitecture in patients with different metabolic disorders.
Methods
A TrueFISP pulse sequence was optimised for high resolution imaging using a 3T Siemens Verio scanner. Images were acquired form the proximal tibia of: seven adults with osteogenesis imperfecta (OI) (ages 21–45) and seven age and sex matched controls (ages 20–45); five teenagers with childhood onset GH deficiency (GHD) (ages 16–19) and five sex matched controls (ages 21–22). Micro MRI images were analysed using in house software developed in IDL.
Results
Patients with OI were found to have a 42% reduction in apparent bone volume (appBV) ($P<0.01$), a 37% reduction in apparent number of trabeculae (appTbN) ($P<0.01$) and a 47% increase in apparent spacing between trabeculae (appTbSp) ($P<0.01$). GHD patients had a 14% increase in appTbSp ($P=0.038$) and 7.4% reduction in appBV ($P=0.024$). Coefficient of variation was low for both intra (appBV 0.55%, appTbTh (apparent trabecular thickness) 0.95%, appTbN 1.02%, appTbSp 1.32%) and inter (appBV 2.09%, appTbTh 2.00%, appTbN 0.87%, appTbSp 1.17%) operator reproducibility.
Conclusion
With the use of routinely available scanning equipment, we have shown there to be differences in the bone microarchitecture between volunteers with OI, where the bones are grossly affected, and controls. We have also shown that this technique is sufficiently sensitive for detecting more subtle changes in bone microarchitecture that may be found in young adults with GHD.

OC2.3

MCM4 mutation causes a novel DNA replication disorder associated with short stature and adrenal failure

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Introduction
A unique variant of familial glucocorticoid deficiency (FGD) exists in the Irish travelling community, a genetically isolated population with high levels of consanguinity. Affected children develop hypocortisolaemia and raised ACTH but retain normal renin and aldosterone levels. Children also have short stature, evidence of increased chromosomal breakage and natural killer cell deficiency.
Methods
We sought areas of homozygosity common to affected patients and subsequently interrogated these areas using massively parallel sequencing.
Results
Targeted exome sequencing identified a variant (c.71-1insG) in mini chromosome maintenance-deficient 4 homologue (MCM4) that is predicted to result in a severely truncated protein (p.Pro24ArgfsX4). Western blotting in patients revealed the abolition of the major 96 kDa isoform, however a minor 85 kDa isoform was preserved. An MCM4 depletion mouse model has grossly abnormal adrenal morphology, with the steroidogenic cortex being infiltrated by GATA4 positive cells significantly reducing the number of steroidogenic cells in the zona fasciculata.
Conclusion
MCM4 is essential for normal DNA replication and genome stability in all eukaryotes. We have identified a mutation in *MCM4* characterising a novel disorder of DNA replication that includes growth retardation, increased chromosomal fragility and variable immune deficiency. In addition this disorder includes adrenal insufficiency and we have shown in mutant mouse adrenals that this can be explained by replacement of steroidogenic cells with non-steroidogenic ones reducing the capacity of the adrenal to produce glucocorticoid. This seemingly specific impact on adrenal function may reflect a defect in adrenal stem cell differentiation.

OC2.4

Short term effects of recombinant IGF1 therapy in children with Laron's syndrome

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Introduction
Children with Laron's syndrome have a classical phenotype which includes extreme short stature and mid facial hypoplasia. It is biochemically characterised by high levels of GH and very low IGF1 levels. These children fulfil the criteria for recombinant IGF1 (rhIGF1, Mecasermin) therapy, however this has to be balanced with possible side effects. This study looked at the short term efficacy and safety profile of six children (five males) with Laron's syndrome who are receiving rhIGF1 therapy in a single regional centre.
Methods
Case notes of all children with Laron's syndrome on rhIGF1 treatment within a single regional centre were reviewed with the primary outcomes being change in height SDS and adverse events.
Results
The median age of initiation of treatment was 9.1 years with median height SDS at start of treatment of −4.9 SDS. The starting dose was 0.04 mg/kg b.d. with dose titration to a maximum of 0.12 mg/kg b.d. over 2–6 months. Duration of treatment has ranged from 0.4 to 1.9 years. The median height increase in four children who have received at least 1 year of treatment was 0.46 SDS. Pre-treatment assessments revealed additional problems in five children (coeliac disease, otitis media, hypercholesterolaemia, pelvic-ureteric obstruction, learning difficulties). The most common adverse events included injection site hypertrophy (4), headaches (2), snoring (1), tonsillar hypertrophy (1) and hair loss (1).
Conclusion
This group of children with Laron's syndrome had a range of additional incidental pathologies and therefore may need increased vigilance irrespective of treatment. RhIGF1 therapy in children with Laron's syndrome has some short term benefit on height SDS scores, with most adverse events related to injection site hypertrophy. Longer term monitoring is essential to provide further information on height outcomes and safety data.

OC2.5

A selective effect of IGFBP3 on brain volumes in healthy children

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Background
GH deficiency is associated with reduction in IQ and neural volumes (globus pallidum and thalamus). Significant relationships between IGF1, IGFBP3 and brain volumes have also been described in children born extremely preterm (total brain volume and cerebellum). No published studies report the relationship between markers of GH status and brain volumes in healthy children.
Methods
Cognitive assessment, MRI brain and measurement of IGF1 and IGFBP3 were performed. Neural volumes were determined. Partial correlation was performed to assess the relationship between IGF1 and IGFBP3 SDS; IQ (controlled for socioeconomic status) and MRI measures (controlled for age, sex and total brain volume). *P* values for significance were adjusted to control for the false discovery rate.
Results
Two hundred and seventy-nine individuals were recruited; 254 children (150 males) underwent both cognitive testing, and measurement of serum IGF1 and IGFBP3 (mean 11.7 years). Of these 254, 161 (99 males) underwent unsedated MRI; volumetric data were available for 95. Neither IGF1 or IGFBP3 SDS correlated with IQ. IGF1 SDS did not correlate significantly with neural volumes. IGFBP3 SDS correlated significantly with right cerebellum ($P<0.02$), globus pallidum (left $P<0.01$, right $P<0.007$) and thalamic (left $P<0.02$, right $P<0.004$) volumes.
Conclusion
We have identified significant correlations between IGFBP3 and pallidum, thalamus and cerebellar volumes in healthy children. Similar relationships have previously been identified in extreme preterm and GH deficient children. This suggests that the association between neural volumes and IGFBP3 is real and that circulating concentrations of IGFBP3 significantly influence brain development. Interestingly, in individuals with GHD we also found a significant relationship between IGF1 and IGFBP3 SDS and IQ. The lack of association between cognitive function and the IGF1 axis in the current cohort suggests that children with a normal GH axis may be less vulnerable to variations in the IGF1 axis than individuals with GH abnormalities.

OC2.6

What defines vitamin D deficiency biochemically in children?

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Background
The level of 25OH vitamin D (25OHD) which separates deficiency from sufficiency is heavily deabted. With decreasing 25OHD levels, typical biochemical derangements set in, such as increasing parathyroid hormone (PTH) and alkaline phosphatase (ALP) levels, and decreasing phosphate and calcium levels. In adults, serum concentrations of PTH reportedly start to rise when serum 25OHD levels drop below 30 μg/l. Such data are scarce in children.
Objective and hypotheses
To determine the concentration of serum 25OHD at which PTH or other bone metabolites start to derange.
Methods
Retrospective audit of blood results from paediatric patients attending our metabolic bone clinic and from our hospital's clinical chemistry dataset. Only patients who had 25OHD, PTH, calcium, phosphate and ALP measured simultaneously were included. Patients with diseases,medications that affect the physiological relationship between the examined biochemical variables, or those with insufficient clinical information were excluded.
Results
The final dataset included 206 children (median age 9.69y). 25OHD ranged from 0.2 to 66.5 μg/l. Of those with 25OHD levels <15 μg/l, 61.9, 33.6, 38.5, 17.8 and 75.2% had biochemical hyperparathyroidism (PTH>50 pg/ml), high

ALP (>1000 U/l), hypophosphataemia (<1.3 mmol/l), hypocalcaemia (<2.2 mmol/l) and any biochemical derangement, respectively. These numbers increased to 71.2, 37.2, 40.4, 19.1 and 82.9% when a 25OHD level of 12.5 μg/l was chosen. All 15 patients with confirmed vitamin D deficiency rickets had 25OHD levels <12.5 μg/l.

Conclusion

PTH levels in this heterogeneous group of patients increased sharply at 25OHD levels <15 μg/l. Nevertheless, a large number of children with vitamin D levels <15 μg/l have no bone metabolic derangement which could be related to a shorter duration of vitamin D deficiency and variable calcium intake.

OC2.7

Selective reduction in trabecular bone mineral density during treatment for childhood acute lymphoblastic leukaemia

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Introduction

Fracture incidence is increased during and after treatment for childhood acute lymphoblastic leukaemia (ALL). Studies using DXA, which measures a composite of both trabecular and cortical bone mineral density (BMD), have shown reduced BMD during treatment. We therefore used peripheral quantitative computed tomography (pQCT) to investigate changes in compartmental (cortical and trabecular) volumetric BMD (vBMD) and bone geometry, and evaluated the influence of treatment factors, adiposity and adipokines on bone outcome.

Methods

Children undergoing treatment for ALL ($n=49$, 65% male, age 9.1±4.0 years) were compared to healthy controls ($n=34$, 50% male, age 9.9±3.7 years). Body composition was asessed by BMI and whole body DXA. pQCT scans were obtained at metaphyseal and diaphyseal sites of the radius and tibia. Blood samples were analysed for leptin, adiponectin and osteocalcin concentrations.

Results

Radial and tibial trabecular vBMD were reduced in subjects with ALL compared to controls ($P<0.05$) but cortical vBMD was unchanged. Tibial bone strength index (BSI), a measure of resistance to compressive forces, was lower in subjects with ALL (54.7±22.2 vs 82.5±27.8 mg/mm^4, $P<0.001$). Subjects with ALL had greater BMI (0.83±1.18 SDS vs 0.17±0.99 SDS, $P<0.01$) and DXA-measured adiposity (32.2±7.6 vs 25.7±7.1%, $P<0.001$) than controls, but no relationships with vBMD or bone geometry were identified. Serum adipokines and osteocalcin were similar in patients and controls.

Conclusion

Selective reduction in trabecular vBMD with excess adiposity may predispose to increased bone fragility. Alterations in adipokines and osteocalcin were not identified as a contributory mechanism to altered bone structure. These findings may inform future choices for bone protective interventions during treatment for childhood ALL.

OC2.8

Novel *SOX2* mutation: from clinical phenotype to identification of new molecular mechanisms of SOX2 action and interactions

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Background

SOX2 is an early developmental transcription factor implicated in pituitary development. It consists of a N-terminal domain, a high mobility group (HMG)-DNA binding domain and a carboxyl-terminal domain. Heterozygous *SOX2* mutations have been described in patients with a severe ocular phenotype and hypogonadotrophic hypogonadism (HH) with/without associated abnormalities. In vitro SOX2 interacts with β-catenin, a member of the Wnt signalling pathway, and represses β-catenin mediated target activation via the carboxyl-terminus. We now report a novel *SOX2* mutation in the HMG domain revealing a distinct mechanism of action.

Case presentation

A female patient first presented at the age of 21 years with primary amenorrhoea (breast stage 2). She had bilateral congenital anophthalmia, developmental delay and HH (FSH 1.0 IU/l, LH 0.6 IU/l, oestradiol <15 pg/ml) with thinning of the corpus callosum on MRI.

Results

Genetic analysis revealed heterozygosity for a novel *SOX2* mutation (c.G261T, p.K87N) in the HMG domain. The mutant protein had comparable transactivation to the wild type (WT) SOX2 ($P>0.5$) and, unlike previous HMG domain mutations, retained its ability to bind to a consensus DNA probe on electrophoretic mobility shift assay (EMSA). Immunostaining confirmed nuclear localisation. However, co-transfection of p.K87N SOX2 with a constitutively active form of human β-catenin (S33Y) in the TOPFLASH reporter assay failed to repress β-catenin mediated activation ($P<0.001$), in contrast to WT SOX2. This may result from altered direct interaction with β-catenin rather than binding to TCF/LEF sites, as we demonstrate that neither WT nor p.K87N SOX2 bind to a TCF/LEF consensus probe on EMSA.

Conclusion

We report a novel *SOX2* mutation in the HMG domain that, unexpectedly, fails to repress β-catenin mediated activation suggesting that the HMG domain is critical for the interaction with β-catenin. We report, for the first time to our knowledge, that clinical phenotypes may result from altered interaction between SOX2 and β-catenin.

Oral Communications 3

OC3.1

The impact of GH deficiency (GHD) and GH treatment (GHTx) on cardiovascular risk in survivors of bone marrow transplantation with total body irradiation (BMT/TBI) in childhood

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Introduction

Survivors of childhood BMT/TBI have increased cardiovascular morbidity and GH deficiency (GHD). We aimed to investigate the relationship between cardiovascular risk and GHD and GHTx in BMT/TBI survivors.

Methods

BMT/TBI survivors ($n=36$) and non-BMT control subjects ($n=19$) were subdivided according to GH status assessed by insulin tolerance test: i) survivors with untreated GHD ($N=18$,11M), ii) survivors on GHTx ($N=18$,10M), iii) controls with untreated GHD ($N=7$,5M), iv) controls with normal GH status ($N=12$,8M). All had body composition assessment (DEXA), and fasted lipids, insulin, glucose, leptin, adiponectin, and IL6.

Results

Results were expressed as mean (S.D.) or geometric mean (range). The ages of the groups were 1.17.1 (6.1–23.5), 2.14.7 (10.9–24.5), 3.12.2 (7.9–15.6) and 4.16.3 (7.8–20.1) years. Survivors with untreated GHD demonstrated increased central adiposity compared with normal controls using LSD but not the more stringent Scheffe test due to group size and heterogeneity (% trunk fat 33.4 (13.4) vs (22.2 (11.1), $P=0.04$). Survivors on GHTx had higher fasted insulin (15.0 (2.6–68.3) vs 5.2 (0.1–48.1) μIU/l, $P=0.05$) and HOMAR (3.29 (0.53–18.31) vs 1.11 (0.02–10.48), $P=0.05$) than survivors with untreated GHD. They also had higher total cholesterol (4.9 (0.8) vs 3.6 (0.7) mmol/l, $P=0.001$) and triglycerides (1.6 (0.5–4.8) vs 0.8 (0.5–1.6) mmol/l, $P=0.03$) compared to normal controls and higher triglycerides than controls with isolated GHD (1.6 (0.5–4.8) vs 0.7 (0.5–1.4) mmol/l, $P=0.05$). Leptin and adiponectin were not different. IL6 was reduced in all groups with GHD i) <0.05 (<0.05–4.73), $P=0.01$, ii) <0.05 (<0.05–14.04), $P=0.01$, and iii) <0.05 (<0.05–19.18, $P=0.05$) compared to normal controls (5.92 (<0.05–39.8) pg/ml).

Conclusion

Adverse cardiovascular profiles persisted in survivors on GHTx, indicating additional factors are involved and alternative strategies targeting cardiovascular risk are needed to improve long-term outcome.

OC3.2

Clinical, genetic, histological and radiological heterogeneity of focal forms of congenital hyperinsulinism

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Congenital hyperinsulinism (CHI) is a cause of severe and persistent hypoglycaemia due to unregulated insulin secretion from pancreatic β-cells. Mutations in the *ABCC8* and *KCNJ11* genes are the most common cause of medically unresponsive CHI. Histologically there are three major subgroups, focal, diffuse and atypical. The pathophysiology of focal CHI is complex and involves a two hit process with the patient firstly inheriting a paternal *ABCC8/KCNJ11* mutation and then with the somatic paternal uniparental isodisomy for the chromosome 11p15 region only within the focal domain. Focal CHI is typically unresponsive to diazoxide and can be cured with complete surgical removal of the focal lesion. We report on three patients with focal CHI to illustrate the marked clinical, genetic, radiological and histological heterogeneity. The first two patients had focal CHI due to a paternal (c.3992-9G>A) *ABCC8* mutation. However one of these patients was fully responsive to a small dose (5 mg/kg per day) of diazoxide and was initially discharged home whereas the other patient was medically unresponsive. In both patients the focal lesions were accurately localised pre-operatively by ^{18}F-DOPA–PET and surgically resected. The third patient had a paternally inherited *ABCC8* (A1493T) mutation and the initial ^{18}F-DOPA-PET scan indicated extensive uptake of DOPA in the body and tail of the pancreas. However despite surgical resection of the body and tail this patient continued to have severe CHI. A subsequent ^{18}F-DOPA-PET scan four weeks later now showed markedly increased DOPA uptake in the remaining body and head of the pancreas. This focal lesion occupied virtually the whole of the pancreas and the patient required a second surgical procedure. These three cases illustrate the complex nature of focal CHI. The clinical observations suggest that focal lesions even with the same genotype (c.3992-9G>A) may have a very different clinical presentation and that ^{18}F-DOPA-PET scans in very large focal lesions may be difficult to interpret. The radiological interpretation of the ^{18}F-DOPA-PET scan in large focal lesion may be difficult.

OC3.3

Laparoscopic near total pancreatectomy for medically unresponsive diffuse congenital hyperinsulinism

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Background
Congenital hyperinsulinism (CHI) is cause of severe hyperinsulinaemic hypoglycaemia in the neonatal and infancy periods. Histologically there are three major subgroups, diffuse, focal and atypical. Patients with diffuse CHI who are medically unresponsive will require a near total pancreatectomy. This has traditionally been performed using an open surgical approach.
Aims
To report our experience of laparoscopic near total pancreatectomy for medically unresponsive diffuse CHI.
Methods
We collected data prospectively on all patients who had undergone laparoscopic near total pancreatectomy for CHI in our tertiary referral Centre between the periods 2004–2009.
Results
A total of 22 consecutive children underwent laparoscopic near-total pancreatectomy for medically unresponsive CHI. The median age at the time of surgery was 3 months (1–120) and median weight was 5.5 kg (4.4–33.4 kg). Seven patients (32%) were converted to open, mostly because of bleeding. There were three common bile duct injuries and no deaths from the laparoscopic procedure. Full enteral feeds were achieved at a median age of 9 days (range 4–17) after the pancreatectomy. Postoperative morphine requirement was limited to the first post-operative day. Octreotide (in decreasing doses) was used in six patients following the laparoscopic near total pancreatectomy. At a median follow up of 46 months (6–86), no patient has required further pancreatic resection. Two children are diabetic and two require pancreatic enzyme replacement.
Conclusion
Laparoscopic near-total pancreatectomy is a novel minimally invasive procedure which is feasible and safe and is associated with prompt post-operative recovery, low complication rate and good outcome. In Centre's with advanced laparoscopic expertise laparoscopic near-total pancreatectomy should be the preferred technique for infants with diffuse CHI.

OC3.4

The heterogeneity of hyperinsulinaemic hypoglycaemia in 19 patients with Beckwith–Wiedemann syndrome due to KvDMR1 hypomethylation

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Beckwith–Wiedemann syndrome (BWS) is an overgrowth syndrome caused by multiple epigenetic and genetic changes. It is due to genetic and epigenetic mechanisms affecting the balance of imprinted genes on chromosome 11p15.5. This region has two imprinted control regions, ICR1 and ICR2. ICR1 contains the genes H19 and IGF2 genes with H19 being maternally expressed and IGF2 paternally expressed. ICR2 contains the KCNQ1, KCNQ1OT1, and CDKN1C genes. Hypomethylation of KvDMR1 (an intronic CpG island within the KCNQ1 gene) on the maternal allele is the most common (about 50%) genetic abnormality observed in patients with BWS. Hyperinsulinaemic hypoglycaemia (HH) is one of the most common biochemical abnormalities observed in patients with BWS. The frequency of HH in patients with BWS varies between 30 and 50% and usually resolves spontaneously but a small group (<5%) may require a partial/total pancreatectomy. The mechanism/s of HH in patients with BWS is/are unclear. The aim of our study was to assess the clinical presentation of HH in patients with BWS due specifically to KvDMR1 hypomethylation. We identified 19 patients with BWS due to KvDMR1 hypomethylation. In this group of patients ten had no HH, five had mild transient (days) HH which resolved spontaneously, and four required diazoxide therapy. None of the patients in this series required pancreatectomy for the HH. Diazoxide was stopped after 6 months in those patients who were commenced on this treatment. Apart from the differences in the presentation of HH these patients also showed marked clinical heterogeneity with respect to the other features of BWS. Macroglossia was the most frequently observed feature with seventeen out of nineteen patients positive for this finding but there was no correlation between extent of macroglossia and severity of HH. Our observations suggest that in patients with BWS due to hypomethylation of the KvDMR1 locus the presentation of HH can be variable, from having no HH to requiring diazoxide therapy. Although the patient numbers are small, HH requiring a pancreatectomy seems to be rare in this group of patients. Further studies are required to understand why patients with BWS due to KvDMR1hypomethylation show marked heterogeneity in the clinical presentation of HH.

Oral Communications 4

OC4.1

Ethnicity rather than deprivation impacts on diabetes control and use of treatment regimen

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Introduction
Delivering an equitable service is one component defining a quality service. Various factors impact on diabetes control including health beliefs and socioeconomic pressures. To determine the role played by ethnicity and/or deprivation we audited access to insulin treatment regimens and overall diabetes control in our clinic population of children and young people with type 1 diabetes mellitus (CYPT1DM).
Methods
Three hundred and twenty-five (170M; age 2–19 years) CYPT1DM were studied. HbA1c measured on four occasions during the year and averaged was used to measure diabetes control. Ethnicity was derived from NHS Standard Demographic Dataset and Deprivation Score (2007) from home postcode. Interactions were sought between ethnicity and/or deprivation and insulin regimen utilised and HbA1c.

Results
Median clinic HbA1c was 7.8% with 2.7% using twice daily (BD), 48.4% multiple (MDI) and 48.9% pump regimens. Average deprivation score was 21.06 which is similar to London. Ethnic proportions were similar to the UK population with a slightly higher proportion of families of African origin. Deprivation score associated with HbA1c ($r=0.14$; $P=0.02$) and were highest in the African and Indian (non-Hindu) groups ($P<0.001$) with a similar trend for HbA1c ($P<0.001$). 52.8% of the white and Indian (Hindu) groups received pump therapy compared to 26.9% of the African and Indian (non-Hindu) groups (χ^2 50.3; $P<0.001$). Although those on pumps had a lower deprivation score (16.39) compared to those on MDI (24.63) or BD (40.51) all the BD were white. In regression modelling 10.0% of the variance in the clinic HbA1c was explained by ethnicity and insulin therapy ($P<0.001$).
Conclusion
These data suggest that ethnicity plays an important role in determining HbA1c but how it influences insulin regimen is unclear. The effect does not appear to relate to deprivation *per se* suggesting health related beliefs in these populations or amongst health care professionals may be operative.

OC4.2

White UK children are older, more obese and more insulin resistant than non-White UK children at diagnosis of type 2 diabetes: baseline results of the UK national type 2 diabetes cohort

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Type 2 diabetes (T2DM) has increased in UK children since the first reports in 2000; however it is poorly characterised and management practice varies across the UK. We aimed to describe the characteristics of the first 103 children recruited to a national study. We wrote to paediatricians asking for children with: diagnosis of T2DM; body mass index (BMI) above 85th centile for age and sex; and other diagnoses such as monogenic diabetes excluded. Clinical data was collected into a national database. Blood was taken for diabetes antibody status. We were notified of 250 affected children and have consented 103 so far. Ten proved antibody positive so were excluded. Of the remainder, the M:F ratio was 1:2.5 and 52% were non-white UK origin (mainly from the South Asian subcontinent). Females were younger at diagnosis (F 11.9 years (S.D. 1.6) vs M 15.8 years (S.D. 1.1); $P<0.001$); and less obese (F mean BMI-*Z* score 2.76 (S.D. 0.69) vs M BMI-Z 3.24 (S.D. 0.88); $P<0.02$. There was a trend for non-white children to be younger at diagnosis (mean 12.5 years (S.D. 2.3) vs 13.2 years (S.D. 2.2); $P=0.07$); and less obese than white UK children (mean BMI-*Z* score 2.68 (S.D. 0.85) vs 3.10 (S.D. 0.71); $P<0.01$. For all the groups, children had fasting or post prandial C-peptide measurements within (50%) or above (50%) the cut points for normal range. White UK children are older at diagnosis than non-White children, more obese, and probably more insulin resistant. 50% of children still have raised C-peptide levels soon after diagnosis of diabetes. This raises the possibility of therapeutic intervention to preserve pancreatic beta cell function early in the disease process.

OC4.3

Non-linear dynamic analysis of glucose regulation in subjects with type 2 diabetes and controls: observed variability and lability (OVAL)

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Introduction
Glucose homeostasis is central to the understanding of diabetes and is influenced by hormones and by substrate flux. This implies a non-linear system which has been confirmed by time series analysis. A dynamic systems approach is required for describing the inter-relationship of glucose and insulin and we describe a method that measures a mathematical domain of glucose homeostasis termed the observed variability and lability (OVAL).
Methods
Plasma insulin and blood glucose concentration profiles were constructed by drawing blood samples every 2 min for 120 min in 12 patients with T2DM median (range) age 35 (25–47) years, duration of diabetes of 7 (2–9) years, receiving oral hypoglycaemic treatment and 30 controls aged 38 (30–53) years matched for gender and BMI.
Insulin and glucose were plotted as consecutive points and the boundary of the relationship was defined as an ellipse. To avoid bias from outliers we used the 95% confidence intervals (95% CI) of the insulin and glucose to define the height and width respectively of the ellipse or OVAL, and the Log_{10} insulin and glucose were normalised by weighting.
Results
T2DM patients demonstrated an increase in the variability of mean (S.D.) blood glucose concentration (0.92 (0.55) mmol/l) compared with controls (0.16 (0.08) mmol/l) ($P<0.001$). Variability of mean (S.D.) Ln plasma insulin concentration was also increased (0.22 (0.67) vs 0.17 (0.07) pmol/l, $P=0.02$). OVAL showed a degradation of homeostasis in type 2 diabetes by a factor of 4 by comparison to controls (OVAL: T2DM 7.8 (3.8) vs controls 1.9 (1.0), $P=0.0003$). The data were not degraded by a sampling interval of 4 min or a reduction in sample size down to $n=4$.
Conclusion
OVAL may enable a complimentary approach towards the examination of the glucose regulatory system that could lead to a better understanding of pathophysiology of abnormal metabolism and as a measure of therapeutic efficacy.

OC4.4

Natural history of background retinopathy in children and young people with diabetes

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Aim
To describe the prevalence and natural history of retinopathy in a cohort of children and young people with type 1 diabetes attending a tertiary hospital diabetes clinic.
Methods
We analysed follow-up data from 2008 to 2010 on all children eligible for retinopathy screening using the 'Twinkle' diabetes database and the regional retinal screening database.
Results
88% (149/169) of eligible children were screened in 2008, median age14 years, 52% male. The prevalence of retinopathy was 19.5% (30/149) (all background retinopathy grade R1). There was significant difference in median (range) duration of diabetes, 7.7 years (0.6–13.7) vs 5 years (0.2–12.5) ($P<0.001$) and median (range) HbA1C, 9.1% (7.2–14) vs 8.6% (5.6–13.1) ($P=0.02$), between the groups with and without retinopathy. At 2 years follow-up, 12/30 (40%) had unchanged retinopathy grade R1, 10/30 (33.3%) showed resolution of changes (R0), 1/30 progressed to maculopathy, and 7/30 had no follow-up data. Median (range) HbA1C in 2008 and 2010 for the groups with stable vs. resolved changes was similar, 9.1% (7.2–14) and 9.2% (7–14) vs. 9.5% (7.8–14) and 9.2% (8.7–14). Of the 119 without retinopathy in 2008, 27 (22.5%) had developed retinopathy within 2 years, including 1 with pre proliferative retinopathy and 1 with maculopathy. There were no significant differences in HbA1c between those who progressed to retinopathy and those who did not, 8.7% (7.1–13.1) vs. 8.6% (6.3–12.2).
Conclusion
The prevalence of background retinopathy in our cohort was comparable to previously published reports, with higher HbA1c and longer duration of diabetes being significant risk factors. On short term follow up, Grade 1 retinopathy is likely to resolve in a third of patients and remain unchanged in just over a third.

Oral Communications (RCN CYP Diabetes Session)

OC5.1

Continuous subcutaneous insulin infusion (CSII) at diagnosis

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The incidence of type 1 diabetes in children under 5 years is increasing. The insulin requirements, eating regimens and reaction to invasive procedures make this group a challenging cohort to manage on multiple daily injections. NICE Guidance was amended in 2008 to include the option of using CSII at diagnosis in the under 5's.

Seven CSII starts at diagnosis have been done (from 2009 to current). CSII is initiated within 72 h from initial diagnosis, following IV insulin, allowing time to discuss treatment options with parents.

We adapted our training programme to allow parents time to adjust to the diagnosis, learn concept of carbohydrate counting, and consider the potential benefits and disadvantages of different insulin regimens. All pump starts have been done in hospital with an average stay of 5 days. Following discharge children and their families are followed up by phone and email – daily for 2 weeks, weekly for 4 weeks before reverting back to routine 3 monthly clinic appointments.

Levels of knowledge and skills of ward staff have an impact on the ability and safety of commencing this treatment at diagnosis. This highlights the need for extra training of ward based nursing and medical staff for this to be a success.

Children achieve improved glycaemic control on CSII compared to MDI. A comparison of modes of insulin therapy has shown 48.3% of children using CSII achieve HbA1c $<7.5\%$ compared to 26.1% of those on MDI (2010). Children using CSII have a higher (mean 65.4) PDQOL than those on MDI (mean 53.3 $P=0.003$).

Emerging evidence on metabolic memory may emphasise the importance of achieving target HbA1c as soon as possible from diagnosis.

OC5.2

Investigating vitamin D status as a determinant of HbA1C% in type 1 diabetic paediatric population

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Maintaining glycaemic control within recommended levels is crucial to minimise vascular complications associated with type 1 diabetes (T1D). Vitamin D is recognised as a vascular growth-factor. Detection of its receptors on pancreatic β-cells suggests it may have a role in glycaemic control. This study aimed to assess determinants of HbA1C including the potential influence of vitamin D status in a T1 diabetic paediatric population.

Methods

Patients attending clinic were recruited. Age, ethnicity, sex, height, weight, HbA1C, insulin dose and duration of diabetes were recorded at each visit from the time of diagnosis. $25(OH)D_3$ was measured at recruitment. To explore the potential relationship between HbA1C and $25(OH)D_3$, we analysed cross-correlation factor (CCF) between mean monthly HbA1C and median hours of daylight per month.

Results

Fifty-three patients (28 males) were recruited (mean age 12.5 years, range 3.7–19.3). Main determinants of HbA1C from time of diagnosis were age and basal-insulin dose u/kg per day ($R^2=0.108$, $P<0.001$). 84% of patients were $25(OH)D_3$ deficient (14.9 ng/ml, range 7.7–26.6) at recruitment. All South-Asian children ($n=11$) were deficient. There was a significant negative relationship between HbA1C at recruitment and $25(OH)D_3$ in Caucasian children ($P<0.01$). Lowest monthly mean HbA1C was in August (8.58%) and highest in December (9.41%). At a time-lag of 0 the CCF was -0.527, indicating a strong inverse relationship. Moving the HbA1C data-series forward resulted in a positive CCF ($+0.109$) at a lead of 3 months.

Conclusion

$25(OH)D_3$ deficiency is prevalent amongst T1 diabetic children, particularly South-Asians. In Caucasian children higher HbA1C was significantly associated with lower $25(OH)D_3$. The cross-correlation data between HbA1C and hours of sunlight suggests a link between UVB radiation (hence $25(OH)D_3$) and control of T1D, with hours of sunlight impacting on HbA1C 3 months later. We suggest that measurement of vitamin D and treating deficiency should be part of regular monitoring in paediatric diabetic clinics.

OC5.3

Use of Peer review to help individual units and networks improve standards of care

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Background

A detailed assessment of children's diabetes services across 21 units in the Y&H SHA identified a significant variation in care with the number of children with an HbA1c $<7.5\%$ ranging from 3 to 30%. This variation could not be explained by demographics or resource.

Methods

Agreement was obtained from three units in Yorkshire to pilot a Peer review visit in conjunction with the national Cancer Peer Review Team and too develop the methodology for Peer review of Children Diabetes services. All three teams were given appropriate support and asked to submit an annual report, operational policy and supporting documents in advance to a trained review team. The chief executive of the trust was informed and half a day was allocated for the visit.

Results

Three children's diabetes services were visited over a 3 day period. I team was identified as the highest performing in the region and two teams who acknowledged they were struggling to improve services. The high performing team had clear governance structures with clear operational policies, downloaded all meters and pumps at the beginning of clinic, had 40% of patients on pumps and 100% on multiple insulin regimens. One of the two teams was identified as having major concerns over dietetic support which was highlighted to the chief executive; both teams had low levels on multiple insulin injections and pumps and had struggled to introduce these to the services due to workload. I team had significant level of deprivation. In neither team had the directorate clearly supported them to improve.

Conclusion

All teams acknowledged the importance of Peer review and felt that it had helped to structure their service and identify a way forward. Peer review is being planned for all services in Y&H region.

OC5.4

A network delivered 'out of hours' specialist telephone support service for young people and families with type 1 diabetes

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Background

Guidelines on standards for diabetes care for children with type 1 diabetes (TID) recommend continuous (24 h/7-day-a-week) access to advice from specialist health-care professionals. However, for many diabetes teams, limited resources precludes provision of this service outside normal working hours. The use of regional networks may enable the implementation of safe, high quality and cost-effective support to patients and families 'out of hours'.

Methods

A prospective 16 week pilot study including five paediatric diabetes centres ($n=965$ TID patients, 15% CSII) located in the East of England. Out of hours (1700–0900 h & weekends) telephone advice for patients was delivered by a team of paediatric diabetes health care professionals (seven clinicians, seven nurse specialists). Advice was given using standardised management algorithms. Calls were logged, and data collected on type / nature of query, advice given and outcome data including hospital attendance and patient satisfaction. Health economic analyses were also performed.

Results

One hundred and ninety-three calls were received from 99 patients ($n=51$M. $n=21$ CSII). Median (range) age 9 (2–17) years. Distribution of calls by centre

ranged from 12 to 28%. 50.5% of calls occurred between 1700 and 2100 h (2100–2300 h (14.6%), 2300–0700 h (5.2%); 0700–0900 h (11.7%), 0900–1700 h (18.%)). Median duration of calls was 9 (range 1–25) min. Reasons for contact were, CSII queries (23%); hyperglycaemia (21.0%), ketonaemia (13%), hypoglycaemia (11%), vomiting (10%), insulin dose errors (6%) and other diabetes related issues (22%). Four calls (2%) resulted in a subsequent emergency hospital attendance. 63 hospital attendances were avoided, with estimated saving of 35.7 in-patient bed days and cost savings of £23K. Mean (s.d.) patient/family satisfaction score (1= poor, 10= high) was 9.7 (0.7).
Conclusion
Safe and effective telephone advice can be delivered 'out of hours' by sharing resources and experience across an established clinical diabetes network with significant cost savings and high patient satisfaction.

OC5.5

Group education facilitation skills for the multidiscplinary team
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Introduction
Currently group education facilitation skills are not part of foundation nurse, medical or dietetic training. Additionally there is no nationally recognised evidence based structured education programme for paediatrics which meet the DoH criteria (2005). Consequently paediatric diabetes teams cannot access group facilitation skills through programmes such as DAFNE and DESMOND in contrast to colleagues working with adults. A one day workshop on group facilitation skills was developed specifically for health care professionals working with CYP through collaboration between a Childrens Diabetes Nurse Specialist, Consultant Diabetologist and an independent, experienced facilitator.
Description/method
Learning outcomes were agreed in advance to ensure a focussed and dynamic workshop for the whole multidisciplinary team and included:- Creating a supportive, interactive and fun learning environment throughout. Building confidence to enhance group facilitation skills. To meet the needs of both CYP and parents facilitating equal involvement of all. Ability to deal with challenging situations arising in groups, including parent-child conflict and dominant individuals. Increased confidence managing monosylabbic teenagers, shy and reluctant CYP, unruly behaviour whilst keeping to the programme and delivering key messages.
Results
Evaluation of this 1 day workshop demonstrated learning outcomes were met in full. Even participants already involved in facilitating groups identified benefits to their practice including increased confidence with challenging family dynamics and across the age groups, a wider repertoire of skills to draw on to manage behaviour, a toolbox of creative activities, along with recognition of the need for full team engagement, less advice giving and more listening.
Conclusion
This 1 day workshop provides an effective and efficient solution to enhance structured education for CYP and families which meets DoH criteria.

Oral Communications (Endocrine Nurse Session)

OC6.1

A service evaluation of children with congenital adrenal hyperplasia (CAH) across South Wales in 2010
Samantha Potter & Justin Warner
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Introduction
Despite 50 years of treating CAH with steroids, clinical practice still varies considerably. In 2002 a consensus statement provided 'best practice' guidelines for the management of the condition. In South Wales CAH is managed by an Endocrine Network. A service evaluation was performed to obtain parents views on their experience.
Methods
Thirty-one patients with CAH were identified. A questionnaire was designed using the consensus statement containing sections on diagnosis, treatment and general service satisfaction.
Results
Ten parents completed the questionnaire (eight female patients). 6/10 found the explanation of CAH at diagnosis good or excellent. In the other four, one had initially been given the wrong gender assignment, two complained of lack of expertise at the initial consultation and one found the whole experience dreadful (like a needle in the head). Only 1/10 had received psychological support at diagnosis. Despite 9/10 finding the explanation of steroid treatment good/excellent, 4/10 reported lack of confidence about emergency IM hydrocortisone usage. Signs of under/over treatment with steroids were poorly understood. Overall all 10 parents rated the service they had received good or excellent with one asking for psychological support.
Conclusion
CAH is a complex disorder and requires considerable expertise. Although most parents were happy with their management a significant proportion were not at diagnosis and highlighted the importance of being cared for by someone who had expertise within the field. CAH should be managed by an MDT with appropriate training. Psychological support for parents of children with CAH is lacking.

OC6.2

An analysis of the clinical and cost effectiveness of GH replacement therapy before and during puberty: should we increase the dose?
Sasha Howard[1,2] & Gary Butler[1,2]
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Background
We aim to investigate the influence of GH on pubertal growth in children receiving GH replacement therapy for GH deficiency.
Methods
We analyse a large dataset of children ($n=236$) with GH deficiency from the international KIGS database. We examine the relationship between pubertal growth and treatment with GH replacement therapy using linear regression and repeated measures analysis, and the incremental cost benefit of increasing doses of GH during puberty.
Results
Multilevel modelling shows that important predictors for height gain after puberty include gender, age at puberty onset and number of injections of GH/week. Cross-sectional analysis of annual change in height SDS in the 4 years pre- and post-pubertal onset suggests that GH dose has a more significant positive influence on height in the pre-pubertal period, with the effect of GH dose post-pubertal onset more marked in girls and children with multiple pituitary hormone deficiencies. Multilevel modelling revealed a highly significant role for GH dose in the pre-pubertal period ($P<0.001$) in comparison to a non-significant effect on height gain after pubertal onset ($P=0.32$). Cost analysis showed that for an average female, use of high dose GH (39 μg/kg per day) at an extra £4,753 per year above the cost of low dose GH (23 μg/kg per day) would result in a gain of ~0.72 cm/year in the pre-pubertal period, compared to a gain of only 0.14 cm/year post-puberty onset.
Conclusion
The influence of GH dose on height gain after puberty onset is at best a modest one. Increasing GH dose to the upper end of the recommended dosage regimen in this period is more likely to have a beneficial effect in girls. Cost analysis reveals that use of high doses of GH after puberty onset has significant cost implications without providing a worthwhile gain in final height for children with GH deficiency.

OC6.3

Paediatric endocrine nurse specialists: roles, education and aspirations
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Introduction
Clinical nurse specialists (CNS) practice at an advanced level of nursing. The Royal College of Nursing (RCN) competency framework for paediatric endocrine

nurses sets out expected levels of practice and academic attainment for 'competent, experienced and expert' practitioners. This paper reports the findings of an initial scoping exercise undertaken to explore current roles, academic attainment and aspirations of this group of nurses in order to inform their future education provision and further research into their clinical roles.

Methods

Utilising the RCN competency framework a questionnaire was developed and sent by post and email to 36 CNS across UK and Ireland. The questionnaire aimed to elicit information about educational attainment, clinical grading, clinical activity, barriers and motivation for further study, and aspirations for development. Data were anonymised prior to analysis.

Results

86% responded.CNS posts are banded between 6 and 8a with no clear delineation of roles between bands. Difference in academic attainment varied from no formal academic study to attainment of MSc and one CNS was studying for PhD. Main motivators to further study were self development or requirements of current post. Barriers to study included family commitments and lack of funding. A significant number indicated that they were not willing to undertake further study as there was no financial benefit or increase in banding available.

Conclusion

Mapping the findings against the RCN competency framework identifies broad variation in clinical activity and responsibilities undertaken by this group of nurses. The resulting role ambiguity is significant for individual security and career progression and role expansion within paediatric endocrinology. Further research needs to be undertaken to strengthen the agreed set of role expectations in the competency framework and develop a national structure for future education.

Poster Presentations

P1

The vitamin D status of Irish children

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Aim
To determine the vitamin D status among healthy Irish children.
Methods
Over a 12 month period (February 2010–February 2011) well children aged 1–16 years attending for minor elective surgical procedures and medical outpatients were recruited. 25 OH vitamin D_3, parathyroid hormone and bone profile were measured and a detailed questionnaire (dietary vitamin D intake, vitamin D supplements, sunlight exposure and Ethnicity) was completed on each patient.
Results
260 healthy children were recruited ranging in age from 1 to 16.2 years (mean 5.8 years). The mean vitamin D level over the 12 month period was 50.5 nmol/l (range 4.8–123 nmol/l) with a mean ($\pm$S.D.) Spring/ Summer vitamin D level of 53.2 ($\pm$26) nmol/l compared to 49 ($\pm$24.5) nmol/l for the Autumn/Winter months. 113/260 (43%) of the group had a vitamin D level $<$50 nmol/l (insufficient) and 40/260 (15%) had a vitamin D level $<$25 nmol/l (deficient).
In the younger subgroup aged 1–3 years, the mean ($\pm$S.D.) vitamin D level was 64.9 ($\pm$22.1) nmol/l as compared to 45.2 ($\pm$22.1) nmol/l in children $>$3 years of age. Twenty percent of all children were receiving vitamin D supplementation. In the supplemented group the mean vitamin D level was higher 57 ($\pm$41) vs 45 ($\pm$31) nmol/l in the unsupplemented group (P value$=$0.05).
Conclusions
Fifteen percent of Irish children in this study have deficient vitamin D levels, with a further 28% of Irish children having insufficient levels. Vitamin D supplementation improved vitamin D levels. Vitamin D sufficiency confers health benefits beyond its primary role in bone health and calcium homeostasis (Hollick NEJM 2007). Supplementation of vitamin D is now recommended for infants in Ireland. This data suggests that vitamin D supplementation should be extended beyond infancy.

P2

Vitamin D supplementation for chronically ill patients: where are we?

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Introduction
'At risk' groups for vitamin D deficiency have long been identified, including the chronically ill. According to guidelines published by the European Society of Endocrinology (ESPE, 2002), the American Academy of Paediatrics (AAP, 2008) and the Endocrine Society (ENDO, 2011), vitamin D levels should be measured in chronically ill or at risk patients. We aimed to test the current knowledge of these guidelines amongst consultants in a large tertiary hospital.
Methods
A questionnaire was emailed to all 176 consultants at Birmingham Children's Hospital. We asked whether they i) routinely check vitamin D levels in chronically ill and 'at risk' patients, and if, how often, ii) routinely supplement chronically ill or 'at risk' patients with vitamin D, iii) if prescribed, which daily dose and duration they choose, and when levels are rechecked, iv) are aware that vitamin D supplementation doses differ from treatment doses, and that exclusively breastfed infants should receive vitamin D supplements.
Results
Of 27 responses (15% response rate), 12 consultants (44%) routinely screen 'at risk' patients. Frequency of screening was inconsistent among specialities (3 monthly to annually). Three specialities routinely supplement vitamin D in 'at risk' patients, one however assuming alfacalcidol was vitamin D. Seventy percent of consultants based their doses on BNF recommendations and levels are rechecked in 6–8weeks by 29%, 3 months by 35%, and 6 months by 11%. 80% were aware that vitamin D treatment and supplement doses differ. Only 8/26 (30%) were aware that exclusively breast fed babies need vitamin D supplementation.
Conclusion
Despite established international guidelines (AAP, ESPE, and ENDO), the knowledge on screening children who are chronically ill or otherwise 'at risk' for vitamin D deficiency was poor within our institution. Regional and national guidelines are needed to improve the long term health of chronically ill children and 'at risk' groups.

P3

Vitamin D deficiency in obese Irish children

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Aim
To determine the vitamin D status of obese Irish children.
Methods
Obese children (BMI $>$97th percentile) attending a weight management programme were recruited over a 12 month period (February 2010–February 2011). 25OH vitamin D_3, parathyroid hormone levels and bone profile were measured. Each patient was matched to a control patient for age, sex and season.
Results
Thirty-one obese children (19 female) were recruited. Mean age was 11.0 years (range 6.2–16.3 years). The mean vitamin D level (S.D.) for the obese cohort was significantly lower (P=0.036) at 39.9 nmol/l (16.1) compared to 47.2 nmol/l (21.3) in the control group. Seventy-four percent of the obese cohort had vitamin D levels $<$50 nmol/l (insufficient) and 22% (7/31) had levels $<$25 nmol/l (deficient). No significant abnormalities were seen in parathyroid hormone levels or bone profile results.
Conclusion
Obese children in Ireland have significantly lower serum vitamin D levels compared to controls. Adult data has demonstrated that both obesity and vitamin D deficiency are linked to cardiovascular disease [1]. Vitamin D deficiency in obese individuals may arise secondary to an increased volume of distribution for fat-soluble vitamin D and a preferential retention of vitamin D in those fat stores. Low serum vitamin D levels in obese children may further increase their risk of cardiovascular disease in later life and highlights the importance of optimisation of their BMI.

1. Cheng *et al*. Adiposity, cardiometabolic risk, and vitamin D status: the Framingham Heart Study. *Diabetes* 2010.

P4

Breaking bones or breaking the bank? A study of vitamin D insufficiency

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Retrospective data collection was performed for all of the paediatric vitamin D (25-hydroxycolecalciferol) serum samples analysed over the preceding 13 months. Around 300 requests were made for vitamin D sampling by various medical professionals including paediatricians (72%), general practitioners (13%), and orthopaedic surgeons (16%). 231 samples, costing £9 per sample, were analysed on 200 patients, predominantly for clinical indications such as growing pains, tuberculosis, and growth failure, amongst others.
Of the 200 patients 112 (56%) were vitamin D insufficient ($\leq$50 nmol/l), of which 25 (22%) were severely deficient ($\leq$20 nmol/l). A significant majority of the vitamin D insufficient patients are of Asian origin (58%), from the inner city, and from deprived areas (full analysis awaited). Bone profiles were sent with vitamin D analysis in the majority of patients: corrected calcium (Ca: n=81; 72%), inorganic phosphate (IPH: n=62; 55%), alkaline phosphatase (ALP: n=80; 71%). 8 of 81 (10%) patients with vitamin D insufficiency had hypocalcaemia; phosphate was normal in all patients. ALP was raised in 4 of 80 (5%) patients, of which only 1 was associated with hypocalcaemia. There was no difference in Ca, IPH or ALP between the insufficient and severely deficient group.
This analysis has demonstrated significant levels of vitamin D deficiency and insufficiency in the paediatric population of Peterborough. The cost implications of testing and management of vitamin D insufficiency is likely to be significantly higher than prevention through supplementation.
There is increasing evidence demonstrating involvement of vitamin D in immunity – particularly in relation to tuberculosis, carcinogenesis, and autoimmunity. It is imperative that a consensus is reached by paediatric endocrinologists regarding definition and treatment of vitamin D insufficiency, and more widely, prevention of insufficiency by supplementation or fortification.

P5

The usefulness of vitamin D measurements in a busy General Paediatric Unit

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Aim
Audit was undertaken to study patient profile, prevalence, treatment choice and interrelation between biochemical markers in vitamin D deficient children.
Methods
Retrospective review of case notes for patients who had vitamin D measured over the period 5/2005 and 5/2010.
Results
Study included 150 randomly selected patients from a total of 336. 99 (66%) were found to be deficient in vitamin D, 52 females and 47 males. Peak age at presentation was 7–11 years, 30% and 12–18 years 24%. Forty-seven percent were of Asian origin, 19% Caucasians, 19% Black and 14% others/unknown. Audited vitamin D test indications included signs of clinical rickets, failure to thrive, gut related pathology (CMPI, atopy related restriction diet, and short gut) and HIV infection. Twenty-five percent were incidental findings. Among the deficient cases 29 had normal/low parathormone and 45 had normal ALP, cCa^{2+} and phosphate with no proportional difference in different ethnic groups. 87/99 were treated, the treatment choice varied – 34 received cholecalciferol, 21 ergocalciferol, 20 - 1 alfacalcidol, 6 dalavit and in 6 treatment was unclear. 24 cases also received calcium supplementation. Follow up and repeat investigations varied in timing.
Conclusion
This audit clearly demonstrates that vitaminD deficiency remains a problem. It continues to be an issue in ethnic minority and clinical high risk groups. Biochemical markers are not always reliable in detecting low vitamin D stores. We are seeing an increase in the request of vitamin D measurements in asymptomatic children. This has led to confusion in the need to treat, treatment choice, follow up and blood tests in these children. With the evolving knowledge about vitamin D role in other disease processes should we investigate more children or recommend maintenance treatment in all children and only investigate the at risk group?
This audit has helped our unit to look at its practise and make some local recommendations in the management of vitamin D deficiency.

P6

Vitamin D status of children and adolescents attending an Endocrinology Clinic

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Introduction
The importance of vitamin D beyond bone health is increasingly recognised. As a result Ireland has recently introduced a policy of vitamin D supplementation for all infants. A vitamin D level of 50 nmol/l for children/adolescents has been recommended as sufficient (1). We sought to establish the vitamin D status in children and adolescents attending a Paediatric Endocrinology Department and explore the relationship between vitamin D status and age, sex, body mass index (BMI) and seasonality.
Methods
A retrospective review of vitamin D levels was conducted ($n=73$). Vitamin D was measured using HPLC mass spectrometry. BMI and age at time of first vitamin D was recorded. BMI *Z* scores were calculated. Data analysed using Minitab.
Results
Seventy-three children (30 boys) were included in the analysis with mean age (s.d.) of 9.0 (5.0; range 1–16 years). Diagnoses included trisomy 21, diabetes, short stature and precocious puberty. Fifty percent of children were classified as overweight or obese. Only 36% had a vitamin D level >50 nmol/l with mean of 40.55 (19.97) nmol/l (range 10–84 nmol/l). There was no difference between boys and girls ($P=0.581$). There was an inverse correlation between vitamin D status and age ($P=0.001$) as vitamin D decreased with increasing age. There was no correlation between BMI and vitamin D level ($P=0.292$). A seasonal effect was evident, with the highest median vitamin D in September and the lowest in December.
Conclusions
This study demonstrates the importance of assessing vitamin D status in the older child and adolescent as only 36% had a level greater than the 50 nmol/l recommended. It is important to consider seasonal effects when assessing vitamin D status. Further study is required to investigate the vitamin D status of Irish children and adolescents to ascertain if the national guidelines for supplementation should be broadened.

P7

Effect of patient choice and hospital tracking on short term growth in children treated with GH therapy

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Introduction
Most (89%) UK units offer some form of free patient choice for new paediatric patients commencing GH therapy. Initial data indicates that patient choice improves adherence, resulting in improved growth (height velocity) short-term.
Objective
To compare outcome measures between patients offered free choice and/or hospital supply (including home services and adherence tracking assessed using ampoule counting) with GH therapy with those who did not.
Methodology
Background data was obtained from the KIGS data base and also hospital notes and endocrine records. Height s.d., height velocity (HV) and HV s.d. were calculated using the growth analyzer version 3.
Results
There were four groups of patients: i) no patient choice but hospital supply ($n=53$). ii) No patient choice nor hospital supply ($n=193$). iii) Patient choice and hospital supply ($n=97$). iv) No hospital supply but patient choice ($n=19$).
Median (95% CI) Δ height s.d. at 1 year of treatment was significantly different ($P=0.03$) between the group offered either patient choice or hospital supply(0.51, (0.43, 0.59)) compared with those getting neither (0.40, (0.33, 0.46)). There was, however, no additional growth advantage conferred by offeringboth patient choice and hospital supply (0.47, (0.37, 0.57) compared to offering just one option (medians 0.53 and 0.59 respectively). There was also no significant difference in Δ height s.d. at 1 year of treatment between the different GH products ($P=0.949$). Height velocity change at 1 year of treatment was not significantly different between the groups ($P=0.319$).
Conclusion
The GH type had no significant effect on change in height s.d. at 1 year of treatment. Receiving either hospital supply or patient choice produced a significant effect in height s.d. at 1 year of treatment compared with neither, but there was no extra benefit in combination.

P8

Audit of diagnostic criteria and growth outcomes over 2 years in children with congenital hypothyroidism

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Introduction
The UK Newborn Screening Programme provide guidelines which facilitate diagnosis and treatment of congenital hypothyroidism (CHT). Prompt treatment is important to ensure normal growth and development. This audit examines initial findings and growth over the first 2 years of life in CHT associated with agenesis, ectopia or dyshormonogenesis of the gland.
Methods
Patients were identified from the University Hospital of Wales paediatric endocrine database and a retrospective case note analysis was performed examining initial investigations and follow up growth data.
Results
39 children with CHT were eligible for the audit. Seven had agenesis, 16 ectopia, 13 dyshormonogenesis and three had transient CHT. The median (range) presenting TSH was higher in those with agenesis and ectopia compared to dyshormonogenesis (482 (83–657), 334 (8–846) and 41 (11.8–981) mU/l respectively, $P<0.01$). After investigation of T_4 therapy, those with agenesis and ectopia took longer for TSH to return to normal (median (range) weeks to TSH recovery 26 (2–39), 24 (2–88) and 8 (2–39) respectively, $P<0.05$). No difference was seen in weight, height and OFC SDS between CHT type at diagnosis and time intervals up to 2 years of age. However, overall from diagnosis to 6 months there was significant 'catch up' weight from a median (range) SDS of -0.52 (-5.6 to 2.0) to 0.21 (-4.0 to 2.1), $P=0.01$. The 'catch up' was greater in

agenesis and ectopia combined compared to dyshormonogenesis (median (range) SDS increase 1.1 (−2.1 to 3.6) compared to 0.2 (−1.0 to 0.54) respectively, $P=0.02$).
Conclusion
CHT due to agenesis and ectopia confer a more severe form of the condition demonstrated by a higher TSH at diagnosis, longer recovery time and significant acceleration in weight during the first 6 months of life. We would suggest that CHT due to agenesis and ectopia require closer monitoring especially over the first 6 months.

P9

A survey of patient/carer opinions and preferences on choice of GH injection device

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Introduction
Approximately 3200 children and young people in the UK receive GH therapy. Currently 12 different GH injection devices are available, with NHS guidance (NICE-TA188) recommending that patients/carers should have a choice of product. Whilst there is evidence that offering such choice may improve treatment adherence, little is known about its importance to patients/carers, nor whether device preferences should be reviewed after a period of treatment.
Methods
Patients receiving GH therapy and/or their carers, attending a tertiary paediatric endocrine centre were asked to complete an anonymous questionnaire about their views and preferences regarding choice of injection device. Where appropriate, preferences were rated one (not important) to five (very important).
Results
100 out 123 eligible patients were randomly approached. 96 patients (mean (range): age 11.8 (1.4–19.0) years, duration GH therapy 3.4 (0–13) years) and carers completed the questionnaire (41 patients, 53 carers). The majority rated choice of GH product at treatment initiation (94%) and the opportunity to review/change GH device after therapy onset (75%) as important (rating 4–5). The most commonly cited attributes for choosing a device were: ease of holding (65%), hidden needle (61%), ready-mixed cartilages (57%), auto-injector (54%), and home delivery service (47%). Preferences for timing of GH device review varied: transition from primary to secondary school (37%), five years (31%) or one year (27%) after starting treatment, and starting college/university (27%). Most (76%) respondents wanted this review to be undertaken at a routine clinic appointment, rather than at a specially-arranged appointment with the endocrine nurses (23%) or through accessing product information (leaflets/DVDs/websites; 11%).
Conclusion
Most young patients on GH therapy and their carers consider choice of injection device to be important and would value the opportunity to review/change device later on. Further research is needed to determine whether this practice affects adherence and long-term treatment outcomes.

P10

A longitudinal study of pubertal growth in inflammatory bowel disease

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Background
Delayed puberty and related problems with growth and body image in Crohn's disease (CD) and ulcerative colitis (UC) have rarely been quantified.
Methods
A longitudinal prospective observational study of children with IBD who had anthropometric and puberty data at 0 and 6 months. Of 50 recruited, there were 15 boys (CDM) and 20 girls (CDF) with CD and ten boys (UCM) and five girls (UCF) with UC. The four groups had a median age at 0 months of 13.4, 14, 13.4 and 13.2 years respectively.
Puberty: Self-reporting performed at 0 and 6 months was compared to the normal reference population to assess for delay in age at onset, Age at G/B1, and progress, Age at G/B3. Two morning salivary testosterone (SalT) samples were collected on 2 days at 0 and 6 months in CDM and UCM and compared to pubertal status and the adult male reference range.
Growth: Height at 0 (Ht0) and Ht at 6 months (Ht6) and height velocity (HV; 0–6 months) were converted to SDS adjusted for pubertal stage (HVPA) and expressed as median (range).
Body Image: Assessed using the IMPACT 3 questionnaire.
Results
The median age of B1 was 11.2 (10, 12.2) and G1 was 11.2 years (10, 11.9) compared to a normal reference population for entry to B2 of 11.2 (9.1, 13.2) and G2 of 12 years (9.7, 14.2). The median age at B3 was 14.1 (11.6, 15.1) and G3 was 13.8 years (10.9, 15) compared to a normal reference population for entry to B4 of 13.2 (10.8, 15.6) and G4 of 13.8 years (11.7, 15.8). In boys, median SalT was <25 pmol/l (<25, 32) in G1, 57 pmol/l (<25, 193) in G2/3 and 228 pmol/l (190, 294) in G4/5 compared to the adult male reference of 216–1370 pmol/l. In G2/3, SalT was higher than G1 ($P=0.05$) and lower than G4/5 ($P<0.0001$). Median Ht0 was −0.15 (−2.6, 0.5), −0.25 (−2.5, 2.1), −0.2 (−1.7, 2.7), and 0.07 (−1.8, 0.4) and Ht6 was −0.23 (−2.8, 0.5), −0.27 (−2.6, 2.1), −0.07 (−1.7, 2.5), and 0.31 (−1.8, 0.4) for CDM, CDF, UCM and UCF respectively. Median HVPA was −0.75 (−7.3, 3.4), −2.3 (−5.1, 5.5), 1.63 (−4.3, 3.3), and 0.4 (−2.4, 4.5) for CDM, CDF, UCM and UCF respectively. In CDF, HVPA was significantly lower than 0 ($P=0.003$). Median body image domain score, using IMPACT 3, showed a significant association with Ht0 and Ht6 (r, −0.31; $P=0.03$).
Conclusion
As a group, disorders of puberty and pubertal growth are more likely to occur in CD, which may have an affect on stature and body image.

P11

Audit of use of transdermal oestradiol for pubertal induction in girls

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Girls with ovarian failure or delayed puberty may be treated with incremental doses of oestrogen to induce puberty. Transdermal natural oestradiol is more physiological than oral synthetic ethinyl oestradiol but it is unclear how effective it is for inducing puberty and whether it confers any benefit.
The aims of the audit were to review whether transdermal oestradiol was effective in inducing puberty, the optimal dosing regimen, effects on breast development & uterine growth, adolescent growth spurt, and the usefulness of serum levels of oestradiol in monitoring therapy.
Twenty prepubertal girls attending a paediatric endocrine unit were studied using a retrospective clinical notes review. Ten girls were treated with transdermal oestradiol (Evorel) and ten girls were treated with oral ethinyloestradiol.
Transdermal group
The median age at start of treatment was 12.7 years, with starting dose 4–12.5 μg. The median height gain was 10.6 cm over 2 years. Three girls had poor breast development. Breakthrough bleeding occurred in five girls at variable doses of oestradiol (6.25–25 μg). Pelvic ultrasound scan in four showed a mature uterus but small in two. The medication was well tolerated. Serum oestradiol levels were variable (<60–278 pmol/l).
Oral ethinyl oestradiol group
The median age at start of treatment was 12.6 years with starting dose 1–4 μg. The median height gain was 14 cm over 2 years. One girl had poor breast development and had compliance issues. Breakthrough bleeding occurred in seven girls at variable doses (6–10 μg). Pelvic ultrasound scan in four girls showed a mature uterus in three, small uterus in one.
Conclusion
Puberty can be induced in girls using transdermal oestradiol. However, further work is needed to establish the optimal dosing regimen. It is unclear whether there are any advantages to the transdermal approach.

P12

The European DSD register: a platform for International Collaborative Research

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Effective research into understanding the aetiology of disorders of sex development (DSDs), as well as long-term outcome of these rare conditions, requires multicentre collaboration often across national boundaries. The EU-funded EuroDSD programme (www.eurodsd.eu) is one such collaboration involving clinical centres and clinical and genetic experts. At the heart of the EuroDSD collaboration is a DSD register that supports the sharing of DSD data. At last review (July 2011) there were 938 cases on the register from 36 centres in 22 countries across six continents. The United Kingdom has the largest number of cases on the register ($n=247$) followed by The Netherlands ($n=179$). The age of presentation ranges from <1 month to 53 years, with a median age of presentation of 10 years. The median year of birth is 1995 (range 1927–2011). The commonest disorder type is disorders of androgen action ($n=282$) followed by disorders of gonadal development ($n=216$). Fifty-nine percent ($n=553$) cases are assigned female sex and 41% ($n=385$) are assigned male sex. There are 18 males with 46XX karyotype and 380 females with 46XY karyotype on the register. There was a history of infertility or parental consanguinity in 7% ($n=68$) and 11% ($n=101$) respectively. Associated malformations were present in 25% ($n=238$) cases. Samples are available in 40% ($n=377$) cases. The majority of cases had a 46XY karyotype ($n=690$), followed by a 46XX karyotype ($n=158$). Mosaicism was present in 6% ($n=57$) cases and a sex chromosome abnormality was present in 1% ($n=8$) cases.

The register has attracted much interest internationally recently and is changing from a European initiative to an international activity. It provides a virtual research environment within which clinicians can interact with each other as well as with investigators and develop new DSD related studies.

P13

The dihydrotestosterone assay for identifying 5α-reductase deficiency: a five-year audit from a UK tertiary Paediatric Centre

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Background

The DHT RIA is often used in the assessment of children with suspected DSD. Affected cases have a history of consanguinity in $\leq 50\%$ and many may not have a non-Caucasian background (Maimoun *et al*., JCEM, 2011). We aimed to assess the clinical utility of the DHT RIA in identifying cases of 5-ARD.

Methods

All DHT requests in a 5 year period in a major UK tertiary paediatric centre were identified and case notes were retrieved and searched to identify the clinical background of each patient, DHT results, rationale for testing and other biochemical investigations performed.

Results

141 tests were performed on 74 patients over 5 years. In 58/74 (78%) patients case notes were available and included 6 (10%) girls and 52 (90%) boys. The median EMS score of these children at birth was 9 (range 0–12). Of the case notes examined all but one patient had DHT levels requested by an endocrinologist. Median age at test was 2 years, (range 1 week–18 years) and median DHT result was 0.37 nmol (range <0.1–2.72 nmol). Twenty-eight patients (48%) had the test as part of 3 days hCG stimulation test, 12 (20%) patients had the test during a prolonged hCG stimulation test, 13 patients (22%) were tested during a routine endocrine screen and 4 (7%) patients were tested for other reasons. In 5 (9%) cases samples were missing at D4 or D22. The median T; DHT ratio at baseline, D4 and D22 was 7 (2.4–94), 13.1 (3.8–40) and 10.6 (5.1–49.3) respectively. Two boys with 5-ARD were identified after testing. These two were brothers of South Asian origin with a history of consanguinity and who had micropenis. The T: DHT ratio in these two cases was 5, 44 and 7, 27 before and after hCG stimulation.

Discussion

Our results question the routine use of the DHT RIA in all boys with XY DSD. The reliability of this test needs to be compared to liquid chromatography-tandem mass spectrometry and genetic testing for SRD5A2.

P14

Height outcome in children with testotoxicosis

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Introduction

Testotoxicosis and other causes of precocious puberty can result in compromised final adult height and various treatments have been used in an attempt to address this. We report final height data in children with testotoxicosis who were treated with a variety of regimens and who have attained/are predicted to attain, a final height in excess of the mid-parental target.

Patients and methods

Growth data from four patients with activating mutations of the LH receptor (4 Met398Thr; 1 Ala572Val) were analysed. An additional boy carried the Met398Thr mutation but didn't develop precocious puberty. Final height data in those with precocious puberty ($n=3$) as well as final and predicted final height data ($n=4$) were compared with UK population norms and mid-parental height.

Results

The mean age at diagnosis was 5.5 years (range 4.3–7.2 years). Three children received treatment that included an aromatase inhibitor (testolactone or letrozole) and one child received the anti-androgen cyproterone acetate with GH. Other agents used included spironolactone and ketoconazole. One boy developed gonadotrophin responses typical of true precocious puberty and was also treated with a GnRH analogue. Mean final height ($n=3$) was 182.3 cm ($+0.68$ S.D.), a mean of 7.7 cm (range 5–10 cm) above the mid-parental target. Mean final height/predicted final height ($n=4$) was 184.5 cm ($+1$ S.D.), 9 cm (range 5–13 cm) above the mid-parental target. All patients achieved final heights above their mid-parental centile but aromatase inhibitors were more successful at normalising height velocity. There were no significant adverse events and adult patients have normal testicular ultrasounds with afternoon testosterone values of 12.2–20.2 nmol/l

Conclusions

Patients with testotoxicosis respond favourably to a treatment regimen that includes aromatase inhibitors and anti-androgens. Only aromatase inhibition was associated with normalisation of growth velocity.

P15

LIN28 in human ovary development and as a candidate gene for primary ovarian insufficiency

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Background

The Lin28 family of proteins are emerging as important regulators of microRNAs in endocrine systems. *Lin28a* influences primordial germ cell development in mice, and overexpression of *Lin28a* in transgenic mice has recently been shown to influence body size, timing of puberty and litter size. The related protein LIN28B is associated with age at menarche and stature in several independent genome-wide association studies in humans.

Aim

We studied expression of *LIN28A* and *LIN28B* in early human ovary development and determined if variations in *LIN28A* are associated with primary ovarian insufficiency (POI).

Methods

Quantitative-RT-PCR and immunohistochemistry were performed in developing gonads. Sequencing of LIN28A was undertaken in 50 women with POI.

Results

Expression studies showed that *LIN28A* was upregulated during a critical stage of early human ovary development (6–9 weeks post-conception, wpc), whereas levels were lower in the developing testis and did not shown any variation over this time period. In contrast, *LIN28B* was expressed at a lower level than *LIN28A*, and did not show differential expression. Immunohistochemistry revealed strong expression of LIN28A in a population of peripheral germ cells in the developing human ovary at 7 wpc. We hypothesized that LIN28A could have an important role in human germ cell development and that disruption of *LIN28A* might lead to germ cell depletion and primary ovarian insufficiency (POI). Mutational analysis of *LIN28A* in a cohort of women with POI did not reveal any significant non-synonymous changes in this gene.

Conclusions

These findings support a role for LIN28A in early human germ cell development, but suggest that changes in *LIN28A* are not a common cause of POI.

P16

GH stimulation testing: how discrepant are its diagnostic tests?

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As the sensitivity of a single GH test is poor, current NICE guidelines (2010) state that to make a diagnosis of isolated GH deficiency (IGHD), two stimulation tests need to show subnormal peak GH levels. In our centre we use insulin tolerance (ITT) or glucagon stimulation (GST) as the 1st test, and arginine stimulation (AST) as the 2nd test.

The purpose of this study was to identify the proportion of children with discrepant test results; and to establish whether lowering the peak GH cut-off might reduce the discrepancy between tests. Our own assay-specific normal peak GH cut off is >5.7 μg/l.

80 children who received two GH stimulation tests in our unit between January 2002 and June 2011 were identified:

Of the 52 with an abnormal ITT, 22 (42%) subsequently had a normal AST.

Of the 28 with an abnormal GST, 7 (21%) subsequently had a normal AST.

The correlations for peak GH levels between the 1st and 2nd tests were moderate, at 0.49 and 0.51 for ITT and GST vs AST respectively.

Lowering the cut off value for the ITT test result to <2.7 μg/l to characterise 'severe' GHD increased the proportion of abnormal second test results from 58 to 68%, but this cut off would miss 15 (50%) children with a peak GH level of 2.7–5.7 μg/l on their 1st test.

In summary, a significant proportion of children have an abnormal 1st test and a normal 2nd test. There is no absolute peak GH cut-off value on the first test that will predict an abnormal 2nd test result. Until a better biomarker becomes available, the NICE recommendation for two GH stimulation tests to diagnose IGHD stands.

P17

GH stimulation tests before and after the introduction of a new GH assay; are we finding a similar proportion of abnormal results ?

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Introduction

We previously used an assay measuring GH levels in microgram per litre. Peak GH levels >20, 10–20 and <10 μ/l representing sufficiency, partial deficiency and deficiency of GH respectively. With a new assay introduced in 2008 peak GH levels >8, 4–8 and <4 μg/l were quoted as normal, partial deficiency and deficiency. Although the patient groups tested were different we would have expected to have approximately similar rates of 'abnormal' results. However, it appeared that proportion of abnormal results was higher.

Aim

To determine if the proportion of results considered abnormal changed following the introduction of the new assay.

Methods

Peak stimulated GH levels measured in microgram per liter, between March 2004–September 2008 were compared those in microgram per liter from October 2008–April 2011. Each test was considered as a separate event. χ^2 test was used to compare the proportions in each category.

Results

46 GH stimulation tests (average 10/years) were carried out in first period, 69 tests (average 26/years) were carried in the second. Normal (>20 μ/l) 45.6%, partial (10–20 μ/l) 30.5% and deficiency GH (<10 μ/l) 23.9%. Normal (>8 μ/l) in 34.7%, partial (4–8 μ/l) 37.6% and deficiency GH (<4 μ/l) 23.1% (no result 4.6%). Although there was a trend towards more abnormal results this was non significant, $P=0.55$. However, had we used cut offs advised by other centres with the new assay (<7 μ/l as deficiency) the proportions of tests would have been 42% normal, 30.4% partial and 23% GH deficiency, i.e. very similar to earlier.

Conclusion

The new assay has highlighted a trend to a higher proportion of tests with abnormal GH on stimulation testing. By changing our diagnostic criteria to that used by other centres this is eliminated.

P18

Novel *KAL1* mutations associated with septo-optic dysplasia in three female patients

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Introduction

KAL1 is essential for GnRH neuronal migration and olfactory bulb development, and mutations within this gene have been implicated in 5% of Kallmann syndrome (KS) cases, a disorder characterized by the association of hypogonadotrophic hypogonadism with anosmia. It is the only identified X-linked form of the disorder and as a result only KS males had been screened for mutations until recently, when females exhibiting KS phenotypes were screened and subsequently tested positive for *KAL1* variations.

Objective

Given apparent overlaps in phenotypes and genotypes between KS and hypopituitarism disorders including SOD and craniofacial defects, we aimed to screen such patients ($n=421$, M:F; 1.1:1) for mutations in *KAL1*.

Methods

Direct sequencing analysis was used to screen the coding region of *KAL1*. Any variants identified were tested using appropriate functional assays. These included investigation of mutational effects on protein secretion analysed qualitatively by immunocytochemistry (ICC) using GFP-labelled KAL1 in Cos7 cells, and western blot analysis.

Results

Three female patients with SOD tested positive for novel mutations in *KAL1*, absent from 480 controls, at highly conserved residues; p.K185N ($n=1$) and p.P291T ($n=2$ (sisters)). All children had optic nerve hypoplasia and GHD, with the p.K185N mutation also being associated with TSHD and an ectopic posterior pituitary. The p.P291T mutation is located between the first two fibronectin domains and we observed a qualitative decrease in secretion of the resultant protein as shown by its retention in Cos7 cells by ICC and western blot analysis. No change in secretion was observed for p.K185N. The p.K185N mutation is located between the WAP and first fibronectin domains of KAL1 and is predicted to affect the binding of the protein to FGFR1 and heparin sulfate. Binding studies are currently ongoing. Both mutations were transmitted by the unaffected mothers. This may reflect variable penetrance or skewed X-inactivation in the affected patients.

Conclusion

We implicate *KAL1* in females with hypopituitarism/SOD for the first time to our knowledge, reflecting an overlap between KS and SOD that has also been observed with *FGF8*, *FGFR1* and *PROKR2* mutations.

P19

Mutations in the Sonic Hedgehog signalling pathway in patients with congenital hypopituitarism

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Introduction

The Gli-family of zinc-finger transcription factors regulates the Sonic Hedgehog (Shh) signalling pathway, critical for normal CNS development. *Gli2* is essential for early pituitary and ventral forebrain development in mice, with mutations described in humans with holoprosencephaly (HPE), isolated hypopituitarism (HP) and cranial/midline facial defects. *SHH* mutations have been associated with phenotypes including HPE but not HP, despite murine studies implicating SHH in early hypothalamo-pituitary development.

Objective

We aimed to establish whether disorders of hypothalamo-pituitary development were associated with mutations in *SHH*, *GLI2*, the highly conserved Shh Brain Enhancer 2 (*SBE2*) and growth-arrest specific 1 (*GAS1*), a membrane bound glycoprotein antagonistic of *Shh* signalling.

Methods

Using direct sequencing analysis we screened 96 HP patients for *GLI2* mutations, 158 HP and HPE-related patients for *SHH* and *GAS1* and 346 septo-optic dysplasia (SOD) patients for *SBE2*.

Results
A novel heterozygous mutation was identified at a highly conserved zinc finger DNA-binding domain residue (c.1552G>A,pE518K) in *GLI2* in a female patient with evolving CPHD (GH and TSH), a small anterior pituitary and absent posterior pituitary. A paternally inherited sequence variant (c.2159G>A, p.R720H) was identified in a conserved region of the *GLI2* activation domain in a patient with a short neck, cleft palate, partial deafness and hypogonadotrophic hypogonadism. A novel mutation (c.1295T>A, p.I431T) was discovered in the C-terminus autocatalytic cleavage domain of *SHH* in two siblings with variable HPE phenotypes, such as a single central incisor. These variants were not identified in 100 controls. No mutations were identified in *SBE2* or *GAS1*.
Conclusion
Our data suggest that mutations in *SHH*, *GAS1* and *SBE2* are not associated with hypopituitarism, although *GLI2* is an important candidate for complex hypopituitarism disorders.

P20

Diabetes insipidus, immunodeficiency and colitis in infancy
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Case history
We report 7 weeks old with central diabetes insipidus, holoprosencephaly (HPE), immunodeficiency and severe colitis. She was first admitted with severe diarrhoea and hypernatremia. A diagnosis of central diabetes insipidus (CDI) was made and she was commenced on subcutaneous desmopressin (DDAVP). Her initial hypothalamic–pituitary axis (HPA) was normal (ACTH 10 ng/l, cortisol 635 nmol/l, GH 23 μg/l and TSH 3.30 μ/l). However repeated cortisols and ACTH were low (cortisol 82 nmol/l and ACTH <5 ng/l) demonstrating HPA dysfunction and she was commenced on hydrocortisone therapy (10 mg/m^2). A diagnosis of hypopituitarism was considered and thus MRI scan was done which revealed lobar HPE. Florid colitis and central salt wasting made electrolytes and fluid balance management difficult. Total parenteral nutrition was continued for 6 weeks with several failed attempts to re-introduce oral feeds. A gastroscopy and colonoscopy confirmed enterocolitis and she was commenced on sulfasalazine 50 mg QDS and probiotic therapy. Over 12 weeks hospital stay she developed three line and two urinary tract infections. Her immunology screen identified very low IgG (0.1 g/l), IgA (0.07 g/l), raised IgM (1.17 g/l) and normal T cell immunophenotype. She was started on intravenous immunoglobulin infusions. IPEX syndrome was considered in view of the combination of immune deficiency, endocrine problems and colitis; however she had normal FoxP3 expression and CD4+CD25+CD127lo cell counts. She was discharged after 3 month on DDAVP and hydrocortisone. Her colitis has stabilised on sulphasalazine and probiotics but she remains on fortnightly immunoglobulin infusions. She has normal developmental milestones to date.
Conclusion
This case report highlights the complexity of managing fluid and electrolyte balance in CDI especially in the light of unresolving colitis. We believe that this is the first case report of CDI, HPE, immunodeficiency and severe colitis in infancy. Genetic comparative genomic hybridisation micro array studies are awaited to clarify this complex phenotype.

P21

Lessons learnt from the management of atypical Cushing's disease
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Cushing's disease (CD) is rare in childhood. There are well described cohorts of patients with classical features. However, given the rarity of CD, we feel it is valuable to share lessons learnt from the treatment of atypical cases.
Case 1
Thirteen-year-old male presented with Cushingoid features. Investigation indicated ACTH excess: 0900 h ACTH 20 pmol/l per cortisol 798 nmol/l; midnight cortisol 724 nmol/l. MRI demonstrated a pituitary macroadenoma (21×16×23 mm). Transsphenoidal adenomectomy (TSA) resulted in biochemical cure (0900 h cortisol <50 mmol/l on three consecutive days). Histology demonstrated a classical ACTH cell adenoma. Six months later GH and cortisol deficiency were diagnosed and treated with good effect: height+1.0 s.d., −1.8 BMI s.d. over 3 years. On a surveillance scan 3 years following surgery there was extensive tumour recurrence with cavernous sinus infiltration and internal carotid compression. There were no clinical or biochemical features of CD.
Case 2
Three-year-old female presented with rapidly progressive Cushingoid features. Biochemical investigations demonstrated ACTH excess: 09.00 h ACTH 12.9 pmol/l per cortisol 748 nmol/l, midnight cortisol 861 nmol/l, 24 h urinary free cortisol 3763 nmol/24 h (NR 50–350). CRH test indicated pituitary disease. Treatment with metyrapone (250 mg od) was followed by a cortisol surge (increase in mean cortisol on five point day curve from 814 to 1779 nmol/l) and acute clinical deterioration. Control was achieved (mean cortisol 146–260 nmol/l) on metyrapone 500 mg qds. TSA resulted in biochemical cure.
Conclusions
i) Pituitary macroadenomas can recur in the absence of clinical and biochemical features of CD. ii) Initiation of metyrapone can result in acute deterioration in CD as the adenoma escapes cortisol suppression resulting in an ACTH and cortisol surge.

P22

What does prolactin measurement add to the evaluation of pituitary hormone function?
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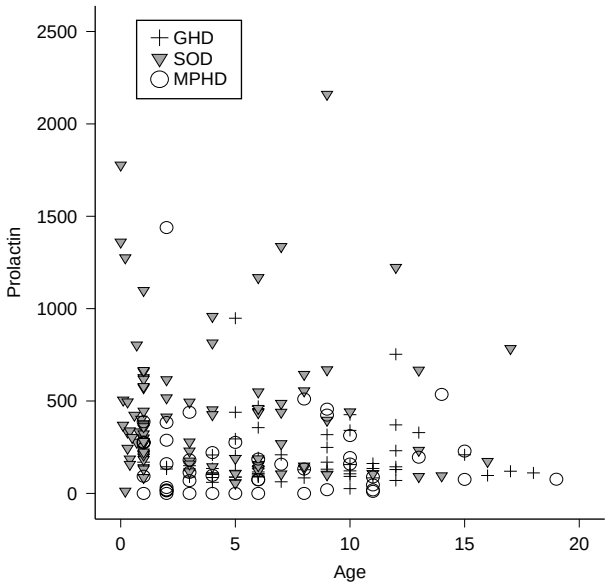
Background
Prolactin concentration is frequently measured as part pituitary function assessment, however there is little published data regarding result interpretation.
Objective
To compare serum prolactin concentrations in children with isolated GH deficiency (IGHD), multiple pituitary hormone deficiency (MPHD) and septo-optic dysplasia (SOD).
Methods
Patients were assigned to the appropriate study group based on the results of their endocrine investigations and MRI brain. (IGHD – peak stimulated GH <6.7 μg/l, MPHD ≥1 pituitary hormone deficiency, SOD ≥2 of; optic nerve hypoplasia, midline brain abnormalities and pituitary hormone insufficiencies), MPHD prolactin assays were performed in duplicate using the Immulite 2500 solid-phase, two-site chemiluminescent immunometric assay. Prolactin concentrations were compared using analysis of covariance, controlling for age at test and sex.
Results
Individuals with SOD had significantly higher prolactin concentrations than those with IGHD or MPHD ($P<0.001$). One child with SOD and 12 with MPHD



had prolactin concentrations $\leq$20 mIU/l. Although the mean prolactin of the IGHD and MPHD patients was the same if all individuals with prolactin deficiency were excluded from analysis the MPHD cohort had a significantly higher mean prolactin than the IGHD group (MPHD, 259 mIU/l; IGHD, 163 mIU/l, $P<0.04$).

Conclusion

It has previously been reported that SOD, which can be caused by mutations in genes involved in hypothalamic development (e.g. HESX1 and SOX3), is associated with hypothalamic dysfunction. A cohort of children with MPHD also appears to have a degree of hypothalamic dysfunction. Although 25% of individuals with MPHD were prolactin deficient, the remainder had a raised prolactin compared to individuals with IGHD. These findings may have implications for understanding the genetic aetiology of MPHD, which so far has only been associated with mutations in pituitary specific genes (e.g. PROP1 and PIT1).

P23

CHARGE syndrome: experience of a tertiary Endocrine Centre

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Introduction

CHARGE syndrome is a complex multisystem disorder with characteristic congenital malformations. The spectrum of endocrine abnormalities associated with CHARGE syndrome is not well defined. We report the experience of our tertiary endocrine centre in the management of these patients.

Methods/study design

Patients with CHARGE syndrome were identified from the endocrine clinic database and information was gathered retrospectively from medical records. *CHD7* was sequenced in patients where DNA was available.

Results

Of the 31 patients identified, medical records were available for 28 patients (11 females and 17 males). The mean age of the patients studied was 14.03 years (5.99–26.25 years). Eighteen were diagnosed with CHARGE syndrome in the neonatal period based on clinical criteria. A mutation in *CHD7* was identified in 9/11 patients tested.

The mean age at referral to endocrinology was 3.6 years (1 month–10.89 years), with short stature being the predominant concern (24/28 patients). Mean height SDS at referral was – 2.4 (-1.2 to -5.63). The mean GH peak on GH provocation testing (performed in 21 patients) was 10.2 μg/l (range 4.3–32 μg/l). Eleven patients were treated with GH. Mean duration of treatment was 9.4 years (range 1–15 years). 16/28 patients (11 males and 5 females) were diagnosed with hypogonadotrophic hypogonadism (HH). Of the 16 post pubertal patients, spontaneous puberty was achieved in two males and three females at a mean age of 11.25 years while seven males and three females required pubertal induction. In two patients hypogonadotrophic hypogonadism was associated with reduced sensation of smell.

Conclusion

Children with CHARGE syndrome have a multitude of endocrine issues amidst other medical problems, and HH is common in this category of patients. Awareness of these issues is important to ensure timely identification and management with prevention of additional morbidity.

P24

A case of familial isolated hypogonadotrophic hypogonadism due to *FGFR1* G687R mutation

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Introduction

Hypogonadotrophic hypogonadism (HH) is a genetically heterogeneous disorder. A number of genes have been implicated in its pathogenesis but, to date, in most cases, the cause remains genetically unknown.

Case

A 14-year old male with delayed puberty (G1P2A3, testes two males) and family history of HH was diagnosed with HH following anterior pituitary assessment and an overnight gonadotrophin profile. His baseline gonadotrophins were low (LH, 0.4 IU/l; FSH, 0.2I U/l) with minimal elevation after stimulation with LHRH (LH peak at 60 min, 0.9 IU/l and FSH 0.4 IU/l). His LH on the profile ranged from 0.3–1.5 IU/l (mean 0.65 IU/l) with only two peaks above 1 IU/l. Pituitary MRI and renal ultrasound scan were unremarkable. After a year of testosterone replacement, his genital and pubic hair development reached stage 3 with testes of six males. He underwent an overnight gonadotrophin profile following stimulation with LHRH. After stimulation, the LH (6.5 IU/l) and FSH (6.4 IU/l) peaks both declined overnight to 0.5 and 2.9 IU/l respectively (mean LH, 3.5 IU/L; mean FSH, 4.65 IU/l), but rose higher after priming to a further LHRH stimulus the following morning (LH, 11.5 and 13.5 IU/l; FSH, 3.5 and 4.9 IU/l at 20 and 60 min respectively), suggesting prolonged hypothalamic LHRH deficiency and intact pituitary gonadotrophins. Screening for mutations in *KAL1, FGFR1, FGF8, PROK2*, and *PROKR2* revealed a maternally inherited mutation in *FGFR1* (G687R) previously described in association with both Kallmann syndrome and isolated HH. His mother suffered from HH and had conceived the proband after 10 years of GnRH therapy. No history of anosmia was reported. Our patient continued on testosterone replacement and is now fully masculinised at 16.3 years but with five males testes.

Conclusion

FGFR1 is implicated in GnRH ontogeny and action. This case report illustrates the autosomal dominant hypothalamic GnRH dysfunction potentially ameliorable with GnRH therapy, that is associated with the *FGFR1* (G687R) mutation.

P25

Limbic encephalitis: a novel presentation of Hashimoto's thyroiditis in children

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Global encephalopathy is a rare complication of Hashimoto's thyroiditis. It typically presents with seizures, ataxia and tremors and responds to steroid therapy. Limbic encephalitis (LE) is even less well described in paediatric population. It presents with medio-temporal lobe symptoms (memory impairment, temporal lobe seizures and disturbances of affect) caused by inflammation within the hippocampus, amygdala, hypothalamus, insular and cingulate cortex. LE most commonly presents as a paraneoplastic phenomenon, although non-paraneoplastic LE has been described. To date, LE in thyroiditis has not been described in children.

A previously healthy nine-year old-boy presented to hospital in status epilepticus, with subsequent encephalopathy. Encephalopathy screen confirmed hypothyroidism (TSH >100, FT_4 8.6, FT_3 4.7) and ruled out alternative pathology. Thyroid peroxidise antibodies were 711 IU/l and ultrasound scan confirmed a vascular goitre. A presumptive diagnosis of Hashimoto's encephalopathy (HE) was made. He developed expressive aphasia, impaired short-term memory and psychosis. MRI scan confirmed evidence of medio-temporal encephalitis with symmetrical progressive high T2 signalling in the hippocampi consistent with LE. EEG showed high amplitude slow waves over posterior quadrant of the left hemisphere. He was subsequently managed with levothyroxine (75 μg daily) and prednisolone. He showed slow clinical improvement and is currently undergoing neuro-rehabilitation.

A recent case series on limbic encephalitis described 10 cases from 12 European centres. Although thyroid peroxidase antibodies were detected in three out of the seven patients, there was no other clinical or biochemical evidence to suggest LE secondary to Hashimoto's disease. Hereby we describe the first paediatric case of limbic encephalitis in Hashimoto's thyroiditis. We propose that MRI scan is the diagnostic method required to confirm this association.

P26

Thyroid isotope scans: can it predict transient or permanent hypothyroidism in babies with borderline TSH values on screening test?

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Introduction

Neonatal biochemical screening programmes for congenital hypothyroidism (CH) allow early diagnosis and treatment of infants with CH, thereby efficiently

preventing mental retardation. The purpose of the study was to assess the predictive role of Tc-99m pertechnetate thyroid scintigraphy in differentiating between transient and permanent hypothyroidism in neonates with borderline TSH results (6–19.9 μ/l) at the screening.
Methods
A retrospective review of 29 neonates (19 males and 10 females) with borderline TSH results at newborn screening between January 2006 and December 2007 was performed. The thyroid scan was acquired 20–30 min after i.v. injection of 1–5 MBq/kg of Tc-99m pertechnetate. Thyroid tracer uptake was graded visually as low (less than equal tosalivary gland uptake), normal (greater than salivary and background uptake) and high (no significant salivary or background uptake seen). The patients were classified in two groups based on thyroxine requirements at 3 years of age. One group included seven children with no requirement of thyroxine replacement (transient hypothyroidism). The other group included 22 children on lifelong thyroxine replacement (permanent hypothyroidism). The pattern of thyroid uptake was evaluated in each group.
Results
Within the group with transient hypothyroidism (seven patients) there was low, normal or high thyroid tracer uptake in 1 (14%), 2 (29%) and 4 (57%) children respectively. The mother of the child with low uptake had raised TSH antibodies. Within the group with permanent hypothyroidism (22 patients), there was low, normal or high thyroid uptake in 3 (14%), 12 (55%) and 7 (31%) children respectively. Only one child had an ectopically located thyroid tissue, the other children had a normally located thyroid.
Conclusion
In this small group of neonates with borderline high TSH on screening the majority of babies with low or normal tracer uptake on thyroid scan had permanent hypothyroidism. Babies with high uptake had either transient or permanent hypothyroidism.

P27

Referral of presumptive cases of congenital hypothyroidism from the newborn screening programme: plain sailing or a choppy ride?

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Introduction
National Standards and Guidelines for referral of presumptive cases of congenital hypothyroidism (CHT) were developed in 2005 by the UK newborn bloodspot screening (NBS) programme centre (UKNSPC). The standards are being revised and NBS lab experience was explored as part of this process.
Methods
A short questionnaire was circulated to all 16 UK NBS laboratories. The information requested included details of referral pattern in the event of a positive or borderline result. Many of the units recruited the help of local paediatricians when completing the form.
Results
All 16 units responded. Most babies were referred to paediatricians, paediatricians with an interest, or more rarely, to paediatric endocrinologists. At one hospital referral was to a Clinical Nurse Specialist. The estimated numbers of health professionals involved per head of screened newborn population varied from 1/1800 to 1/120 000. Most paediatricians were unaware of the standardised information for families provided by the UKNSPC. Those who offered information leaflets to families used those on the BSPED website or the Child Health Growth Foundation's general thyroid booklet. The time from parents hearing of results to clinic appointment was usually 1 or 2 days. Referral to a large number of different individuals was considered to be unsatisfactory because of the extent to which clinicians were uncertain about how to manage the clinical scenario with the duty biochemist frequently guiding the clinician.
Conclusions
The number of health professionals to whom babies with positive CHT screening test results are referred should be limited. There needs to be a named individual with an identified deputy who form part of a network with support from a tertiary centre as necessary. Updated, standardised parent information leaflets should be more readily available.

P28

Prophylactic thyroidectomy in children with MEN2 in the United Kingdom

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Introduction
Timing, extent, complications rate and long term results of paediatric prophylactic thyroidectomy (pPT) for MEN2 in the UK are unknown.
Methods
All UK centers performing pPT were invited to participate in the study.Data were obtained from notes and hospitals electronic databases.
Results
Fifty-one children (27 males) were included.All had genetic test at the mean age of 5 years (median 3, range 0.25–15), confirming 45 MEN2 and 6 FMTC. Mean baseline preoperative calcitonin was 27.34 (median 12, range 0–290). Ten patients underwent preoperative pentagastrin stimulation test. Fourty-seven had surgery (47 total thyroidectomise, of which three had central and one lateral nodes dissection) and four are awaiting operation. Surgery was performed at a mean age of 7 years (median 5.47, range 0.74–20.88). Postoperative calcium was low in 65% of children but only eight required prolonged calcium treatment. Respiratory distress with aspiration pneumonia developed in the only patient who had bilateral neck dissection. Histology was available in 42 cases (17 medullary cancers, 22 C-cell hyperplasia and 3 normal thyroid glands). In seven patients lymph nodes were examined at histology and all were found negative. Median follow-up was 35.95 months (range 0, 2–142).There were no relapses. At year 1–5 postoperative calcitonin was detectable in 4/26 (4 out of 26 tested), 7/15, 8/15, 2/4 and 2/5 children respectively.At year 2–5 it was elevated in one, two, two and one children respectively.
Conclusion
pPT is a safe procedure,with a low rate of postoperative complications. Commonest operation was total thyroidectomy without lymphadenectomy. Timing of surgery is guided by RET mutation and basal calcitonin levels rather than pentagastrin stimulation. The relevance of detectable and marginally elevated levels of postoperative calcitonin in uncertain and only long term follow up will give us insight into its significance.

P29

Audit on initial management of congenital hypothyroidism

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Aim
To audit the current congenital hypothyroidism (CHT) management practice in our centre.
Standards
Guidelines published by UK Newborn Screening Policy and Standards in 2005 and ESPE in 1999.
Method
Retrospective audit from 2006 to 2010. The list was compared with the regional newborn screening lab to ensure data collection was complete.
Results
Thirty cases were referred to the unit giving local incidence of 7/10 000 births compared to 2.5/10 000 in UK. 28/30 were identified on Guthrie test and 2/30 on prolonged jaundice screen with normal Guthrie test. 67% were females. 50% were of South Asian (SA) ethnicity, 37% White Caucasian (WC) and 13% others compared to the local birth ethnic figures of 20% SA, 65% WC and 15% others. Data of 29 children were analysed (one child died related to prematurity complications). All had blood test to confirm diagnosis. 19/29 (65%) had thyroid radioisotope scan of which 52% demonstrated normal uptake (possible

dyshormonogenesis) and 38% lingual/absent thyroid. 22/29 (75%) had CHT confirmed and 7/29 (25%) subclinical hyperthyrotropinaemia (SHT). Thyroxine tablet preparation at daily dose of 37.5 or 50 μg was used except 8/22 on 25 μg daily dose (< 10 μg/kg per day). 7/8 who received 25 μg dose showed a pattern of delay in normalising TSH confirming inadequate dosage. Of the seven cases with SHT (TSH range from 5.1 to 36 mIU/l – reference = 0.3–5 mIU/l), 3/7 went on to develop CHT requiring treatment (one had lingual thyroid) and 4/7 eventually normalised (range 5–28 weeks age).
Conclusion
The incidence of CHT in our local population is higher than the national figure with an increased incidence amongst SA. Initial thyroxine dose of < 10 μg/kg per day (25 μg once daily) is inadequate. Two cases of CHT diagnosed on prolonged jaundice screen would not have been picked up if the recently published NICE guideline on jaundice was followed.

P30

Phenotypic variability of 17α-hydroxylase (CYP17A1) deficiency

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The steroid 17α-hydroxylase enzyme CYP17A1 exerts two distinct activities that catalyze conversion reactions at key branch points in steroidogenesis. CYP17A1 17α-hydroxylase activity is the key step in cortisol synthesis whereas CYP17A1 17, 20 lyase activity generates sex steroid precursors. Inactivating CYP17A1 mutations result in CYP17A1 deficiency (17OHD), a rare form of congenital adrenal hyperplasia that classically presents with combined glucocorticoid and sex steroid deficiency and hypokalaemic hypertension.
We have investigated four patients with 17OHD harbouring four novel mutations, which we analyzed *in vitro* and *in silico*. Case 1 (46,XY; homozygous p.F53/54del) presented at 12 years with glandular hypospadias, gynaecomastia and cryptorchidism. Endocrine assessment revaled hypergonadotropic hypogonadism, low cortisol at baseline and after $ACTH_{1-24}$ stimulation, but notably normal blood pressure. Case 2 (46,XX; homozygous p.Y60I*fs*K88X) presented with severe adrenal insufficiency three weeks after birth. Case 3 (46,XX; p.G111V/p.P409L) presented at the age of 15 years with lack of pubertal development and a history of hypokalaemic hypertension since the age of 2 years. Case 4 (46,XY; p.R347H/p.A398E) was born with ambiguous genitalia but had normal blood pressure and no evidence of glucocorticoid deficiency at the age of 24 years. Urinary steroid profiling with gas chromatography/mass spectrometry established the biochemical diagnosis in all cases. Functional *in vitro* analysis of CYP17A1 activities in transiently transfected HEK293 cells confirmed p.Y60IfsK88X and p.P409L to abolish CYP17A1 function; p.A398E, p.F53/54del and p.R347H resulted in mild to moderate impairment of enzyme activity. Results of *in silico* analysis of the identified mutations were consistent with the *in vitro* findings.
In summary, we have identified four novel *CYP17A1* mutations and our functional studies confirmed the pathogenicity of these mutations. The clinical presentations ranged from neonatal presentation with severe adrenal insufficiency to delayed pubertal development and normal adrenal function, illustrating the broad phenotypic spectrum in 17OHD.

P31

Oxidative stress in the pathogenesis of Triple A syndrome

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Introduction
Triple A syndrome is a rare, autosomal recessive cause of adrenal failure that usually manifests in the first decade. Most cases have isolated glucocorticoid deficiency, but this is accompanied by mineralocorticoid deficiency in ~10%. Additional features include alacrima (~90%), achalasia of the oesophageal cardia (~75%), and a progressive neurodegenerative process (~60%). The *AAAS* gene product is the nuclear pore complex protein ALADIN of unknown function. Previous studies have described dermal fibroblasts from AAAS patients as being more sensitive to oxidative stress than wild-type fibroblasts.
Methods
To provide a better disease model we have successfully achieved knockdown of *AAAS*-gene expression in H295R adrenocortical tumour cells (chosen as representative of the cell type affected by AAAS) using synthetic shRNA lentiviral transduction. To assess the adverse effects of oxidative stress, cells were exposed to hydrogen peroxide.
Results
Without hydrogen peroxide treatment there was significantly reduced cell growth, both by cell counting ($P<0.05$, $n=4$) and the use of MTS assays ($P<0.05$, $n=3$), of *AAAS*-knockdown cells in comparison with controls. These cells, when treated, show significantly reduced cell survival in comparison with controls ($P<0.05$, $n=3$). An increase in apoptosis was observed, assessed by cleavage of PARP (poly ADP ribose polymerase), of *AAAS*-knockdown cells after treatment compared with control cells ($P<0.05$, $n=3$).
Conclusion
Using *AAAS*-knockdown cells we provide further compelling evidence that oxidative stress is involved in the progression of Triple A syndrome. As the steroidogenic activity of the adrenal cortex induces a highly oxidative environment this may explain the susceptibility of the tissue in the absence of functional ALADIN.

P32

Steroid dose, age and gender affect adrenal responses to a low dose short Synacthen test in children with asthma

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Background
The activity of the hypothalamic–pituitary–adrenal axis (HPA) during inhaled corticosteroid (ICS) treatment of asthma has been studied extensively. To date patient populations have been too small or homogeneous to identify relationships between steroid exposure, patient characteristics and HPA activity. In this abstract we report data from a large, heterogeneous cohort of patients recruited to observational and pharmacogenomic studies.
Patients and methods
A simplified low dose short Synacthen test (Synacthen dose 500 ng/1.73 m^2, sampling at 0, 15, 25, and 35 min) was performed in 332 subjects (201 M, age 11.2 ± 3.3 years) treated with ICS for > 3 months. Patients treated with prednisolone daily were excluded. Total steroid exposure (TSE; inhaled + intranasal + oral) was calculated as beclomethasone equivalent in ratios of 1:1 (clenil modulate, budesonide), 2:1 (fluticasone) and 3:20 (prednisolone) and adjusted for body surface area (BSA). Median TSE was 813 (25th/75th percentile: 400/1183) μg/day.
Results
Cortisol response was impaired (peak cortisol < 500 nmol/l) in 115 subjects (34.6%). Basal (252 ± 140 nmol/l) and peak (554 ± 154 nmol/l) cortisol correlated negatively with BSA adjusted TSE ($P=0.009$). Age and gender associated positively with basal and peak cortisol (age: $P=0.0002$, gender: all ages $P=0.015$, age > 12 years $P=0.003$). Time to peak cortisol was positively associated with value of peak cortisol ($P=0.003$).
Discussion
To our knowledge this is the first study to consider the effect of TSE rather than ICS in isolation. Our observation that female gender and greater age are associated with higher basal cortisol may reflect an oestrogen driven rise in cortisol binding globulin during female puberty. We speculate that the relationship between time and magnitude of cortisol peak reflects more rapid depletion of cortisol in adrenals with lower cortisol reserve. These data give interesting insights into the maturation of the HPA during childhood and adolescence.

P33

Towards a non-invasive short Synacthen test

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Introduction
A 2009 BSPED survey revealed that 90% use a low dose Synacthen test (LDST) and 44% had noticed increased referrals of asthmatic children prescribed inhaled corticosteroids (ICS). Approximately 21% of UK children have asthma of whom 70% are prescribed ICS (10% at 'high dose'). There is an increasing need for a simple, less invasive, alternative to the LDST to evaluate their adrenal function. We are developing a non-invasive LDST, with Synacthen administered nasally and cortisol measured in saliva.
Methods
We performed three Synacthen tests on 12 healthy, adult males. On the first visit volunteers received 1 μg i.v. Synacthen, the second and third visits 100 and 25 μg intranasal Synacthen respectively. During a 3 h test 14-paired samples of blood and saliva were taken. All volunteers were dexamethasone suppressed enabling us to measure Synacthen on an ACTH RIA.
Results
We achieved a median $AUC_{0–180\ min}$ with 100 μg intranasal Synacthen, 20% of that following a 1 μg i.v. dose, (6% with 25 μg), this gave a bioavailability of 0.2–0.24%. The C_{max} was 17.9 and 11 pg/ml respectively compared with 169 pg/ml i.v. T_{max} was 17.5 and 10 min respectively compared with 5 min i.v. On analysis of the 1 μg i.v. data we observed considerable variability in mean peak plasma Synacthen (261.6 pg/ml S.D. 104.9). The timing of the peak cortisol varied, occurring at 30 min in 50%. There was no relationship between peak Synacthen and peak cortisol, despite correction for BMI and BSA. None of our participants achieved a cortisol above 450 nmol/l, which we believe is a blunting effect of dexamethasone.
Conclusion
We have shown considerable variability in the 1 μg i.v. LDST. The doses of intranasal Synacthen chosen in our study did not reach bioequivalence with the 1 μg LDST. However the test was well tolerated and easy to administer and so with increased dose holds considerable promise.

P34

All Wales steroid card: the way forward

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Introduction
Children on long-term steroid replacement for adrenal insufficiency may need emergency administration of i.m. hydrocortisone when unwell. There was a recent incident in Wales in terms of the out of hospital administration of hydrocortisone by ambulance crew. A child on long-term hydrocortisone for hypopituitarism became unwell at school. When the ambulance crew attended, it was brought to our attention that they cannot administer i.m. hydrocortisone unless the underlying diagnosis is Addison's disease!
Discussion
Majority of paediatric patients who require steroid replacement do not have Addison's as the underlying diagnosis (i.e. have adrenal insufficiency from other causes), this therefore causes a potential delay in emergency treatment to a large group of patients. This is, despite all ambulance teams carrying hydrocortisone as part of their emergency equipment. All the UK ambulance trusts follow the same guidelines and therefore this is a potential problem for the whole of UK.
The way forward
We wrote to BSPED –- as a group representing paediatric patients with endocrine conditions in the UK – to try and remedy this problem by highlighting this to the ambulance guidelines committee so that future publications may be amended. It should be clear that any patient on long term steroid replacement may present in an 'adrenal crisis' at times of illness. A dose of intramuscular hydrocortisone should be considered in these circumstances.
In the interim period within Wales we are registering patients on long-term steroid use with the ambulance trust so that there is an alert on the system to highlight the potential need and thereby prevent adverse incidents.
We are also developing an 'All Wales steroid card' in conjunction with the Welsh Ambulance Trust so that this may be recognized and acted upon by the attending paramedic. This may be later adopted all over the UK, if found useful.

P35

Extreme hyponatraemia with intact neurological outcome in a young child with Addison's disease

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Introduction
Hyponatraemia presents a diagnostic challenge in acute medicine. Suggestive symptoms may be present or it can be an incidental finding. Whether it is acute or chronic, associated with excessive, normal or reduced intravascular volume all help determine cause and correct management.
Case report
A six-year-old boy with a good neurological outcome from extreme hyponatraemia (initial sodium 96 mmol/l) caused by autoimmune hypoadrenalism. He presented with one week of reduced appetite, lethargy, vomiting, and one episode of diarrhoea. He was described as being slightly unsteady on his feet.
Examination
Alert, although intermittently confused, with dry mucous membranes and sunken eyes. Clinically 10% dehydrated, serum sodium was 96 mmol/l with normal serum potassium and renal function.
Cortisol (283 nmol/l) at presentation was considered suspiciously suboptimal for degree of illness. He was initially treated with 3% saline i.v., and by day 3 serum sodium increased to 128 mmol/l. Day 4 he developed slurred speech and ataxia, although MRI brain showed no evidence of pontine myelinosis. Symptoms resolved over one week. Interestingly, a further random serum cortisol on day 8 was reassuringly normal (607 nmol/l), although hyponatraemia persisted (131 mmol/l). Primary adrenal failure was diagnosed based on flat Synacthen test response: cortisol 198 nmol/l (0 min), 196 nmol/l (30 min) and 212 nmol/l (60 min), elevated ACTH 314 ng/l, and an extremely elevated plasma renin 1110 μ/l (normal 4–85 mU/l). Investigations into the aetiology showed normal very long chain fatty acids levels excluding X-linked adrenoleukodystrophy, but positive adrenal autoantibodies identifying an autoimmune process. He commenced hydrocortisone and fludrocortisone replacement therapy. At 8-month follow-up there are no obvious neurological or developmental sequelae.
Conclusions
This case illustrates i) the surprisingly young age at which autoimmune adrenal failure can present, ii) important principles of fluid resuscitation in extreme hyponatraemia, iii) differential diagnoses to consider, and iv) that neither normal serum potassium nor detectable random serum cortisol exclude Addison's disease.

P36

Recurrent hypoglycaemia with hyponatraemia during illness: what lies beneath?

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Hypoglycaemia is a one of the commonest presentation of an ill child. Hyponatraemia during illness is mostly presumed to be related to syndrome of inappropriate anti diuretic hormone secretion (SIADH). We would like to present an interesting case of hypoglycaemia and hyponatraemia.
A four-year-old boy presented with a two-day history of intermittent fever, vacant episodes, and seizures. He was noted to be hypoglycaemic with laboratory glucose of 1.2 mmol/l and sodium of 124 mmol/l. He was treated with intravenous dextrose, and subsequently chest X-ray suggested bilateral pneumonia. He was treated for this with antibiotics and dextrose. He had a further episode of hypoglycaemia and subsequently he made a full recovery with sodium and glucose returning to normal. A Synacthen test and glucagon stimulation test showed a flat curve of cortisol response. His ACTH was 4083 ng/l (range 0–50). His hypoglycaemia screening blood tests were normal.
His mother later gave a history that he does not form tears on crying, suggestive of alacrima. He was previously healthy apart from daily episode of persistent effortless vomiting starting at age of 2 year. Investigations ruled out gastro-oesophageal reflux apart from a finding of tight pylorus on endoscopy. He is due to undergo further investigation of lower oesophageal sphincter to confirm clinical diagnosis of achalasia. He has been commenced on Hydrocortisone, and his hypoglycaemia has not recurred yet.
We suspect him to have the 'AAA' (Algrove) syndrome, which consists of a triad of adrenal insufficiency, achalasia of the cardia, alacrima. It has been associated with the abnormalities of AAAS gene on chromosome 12q13.
This case reflects the need for a full history and tangential thinking in unusual clinical situations like hypoglycaemia and hyponatraemia in a young child.

P37

Second primary tumours in young adult survivors of childhood posterior fossa brain tumours and prior therapeutic protocol

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Background
SPT are late effects of childhood PFBT. Low dose radiation scatter at the edge of craniospinal field has traditionally been blamed for meningiomas and thyroid tumours but the effect of chemotherapy, genetic predisposition and GH replacement on their prevalence is less clear.
Methods and aims
As part of a descriptive study of long term (>10 years) functional, endocrine and cognitive outcomes in 36 (20 males) adults aged 21.2 (16–32) years, of whom 34 had childhood GH after surviving therapies for PFBT at 6.9 (0.1–16.6) years, we performed surveillance MRI Brain scans. We also recorded non-CNS SPTs, prior oncological therapy and genetic predisposition.
Results
Over a median 14.7 (9.3–27.4) years follow-up, we documented ten SPT in seven patients – all of whom had prior craniospinal irradiation as well as two screen-detected cavernomas. One patient had two SPT's before 16 years of age (thyroid Ca and bowel) after a medulloblastoma (MB) at 5 years and was found to have familial *APC* gene defect. Another treated for MB at 2 years with additional chemotherapy had BCC, thyroid adenoma and asymptomatic meningioma, all resected before 32 years of age and had never received childhood GH. Five other patients had one SPT each; three screen-detected meningiomas (two resected, one with prior chemotherapy), and two BCC's.
Conclusion
Approximately 20% (1:5) of our PFBT cohort developed at least one SPT within a median 15 years period, of whom 2 (0.5%), – one with a familial predisposition, the other with additional chemotherapy (and no GH) had more than one. Excepting the familial patient, all SPTs were low grade and curable by surgery. These data are useful baselines against future changes in prevalence with increasing use of high intensity adjuvant chemotherapy can be potentially assessed. It is unlikely that GH treatment has contributed.

P38

Endocrine, cognitive and visual outcomes following treatment for Craniopharyngioma at a single institution: a prospective observational study

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We prospectively assessed endocrine, cognitive and visual outcomes in eight (three males) craniopharyngioma (CP) patients aged 7.98 (range 2.45–14.15) years presenting to our centre over the last 18 months, according to initial risk-based surgical strategy. Four patients had incomplete debulking (GpA), and four had conservative cyst decompression surgery (GpB). One patient (GpB) recurred 8 months later and needed repeat cyst decompression surgery. Four patients (two from each Gp) had adjuvant radiotherapy (DXT) delivered as protons in two cases.
BMI increased (mean increase of +1.05 SDS and 0.56 SDS by 2–9 months and >9 months respectively) post operatively in all but was worse for GpA. All GpA patients were rendered panhypopitiutary (with DI) by surgery, before DXT, whereas 3/4 GpB patients currently have intact HPA function, and one developed panhypopitiutarism and DI shortly after conservative cyst decompression surgery (and before DXT). 3/8 patients (GpA=2; GpB=1) presented with visual field defects, one (GpA) progressing to unilateral blindness post-operatively. All our patients attend mainstream schools with normal neuro-development.
Despite the rarity of CP we have managed eight new patients over 18 months on a risk-based surgical strategy and demonstrated that conservative cyst decompression surgery demonstrably preserves pituitary (and visual) function but does not prevent a rapid post-op increase in BMI, although this is less marked than after debulking surgery. Longer-term follow up will serve to show if recurrence is also minimalised and intellectual function preserved.

P39

Treatment strategies and outcomes of paediatric Craniopharyngioma since 2005: a single centre experience

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Background
The Craniopharyngioma service in our centre has changed since 2005 with a standardised preoperative assessment and a new approach to surgery and use of radiotherapy. We review the subsequent outcomes.
Treatment strategy
Preoperative endocrinology: prior to dexamethasone therapy: standard dose short synacthen test (SST), thyroid function test (TFT), IGF1, LH, FSH, testosterone/oestradiol±GH stimulation test. Staging: MRI and tumour staging (Paris classification). Cystic lesions: endoscopic decompression (ED)+repeat MRI+reclassification. Surgery: total (TR), near-total (NTR) or subtotal tumour resection (STR) determined by Paris stage. Radiotherapy: elective for residual disease in older children. Postoperative endocrinology: 5–7 days following dexamethasone: 0900 h cortisol+ACTH, low dose SST, TFT. 3–6 months: anterior pituitary function tests.
Results
Data from 23 subjects (10 M), age (median and range) 10.9 years (1.5–15.5) are reported. Treatment: ED: ($n=13$) seven tumours downgraded following ED. Surgery: TR 5/23, NTR 5/23, STR 11/23, awaiting surgery 2/23. Radiotherapy: 9/20 (four following tumour progression/recurrence). Auxology: baseline ($n=22$): height SDS, 0.89±1.55; BMI SDS, 1.46±2.53. Greater than equal to 6 months ($n=18$): height SDS, 0.71±1.51; BMI SDS, 1.61±1.91. Endocrinology (patients tested/patients abnormal results): i) baseline: SST 19/8, TFT 23/3, IGF1 19/10, GH 2/2, LH, FSH 15/13, diabetes insipidus (DI) 24/0. ii) Follow-up: SST 17/12, TFT 17/17, IGF1 15/10, GH 16/15, LH, FSH 17/12, DI 21/17, panhypopituitarism 17/10.
Conclusions
Pituitary hormone deficiencies are common at presentation and progress following treatment. ED led to downgrading of some tumours. This enabled more extensive resection in 50% of patients, and reduced use of radiotherapy, but short-term outcome data are comparable with previous studies.

P40

Gonadal failure in children with acute lymphoblastic leukaemia treated by bone marrow transplantation: prevalence and risk factors

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Background
Gonadal failure is a well-recognized long-term complication of bone marrow transplantation (BMT) in children with acute lymphoblastic leukemia (ALL). Identifying key risk factors is helpful in planning and counselling for hormone replacement therapy (HRT) and in targeting future research.
Objectives
To determine the prevalence and risk factors for primary gonadal failure (PGF) in childhood ALL treated with BMT in a single centre.
Methods and patients
Retrospective study of 108 patients treated from 1989-2009. Of 54 survivors, 40 (25 M and 15 F) aged 22.6 (11–32) years were analysed after excluding patients with insufficient data (4) or BMT carried out <2 years previously (10). BMT was performed at 9.4 (range 2.3–17.3) years, using high-dose chemotherapy with alkylating agents, mainly cyclophosphamide, and total body irradiation (1440 cGy in eight fractions). PGF was defined as basal FSH and LH >10 IU/l in pre-pubertal; FSH >16 and LH >18 IU/l in post-pubertal patients.
Results
The overall prevalence of PGF was 83%. All females were affected irrespective of pubertal status at the time of BMT (eight prepubertal, seven pubertal/post-pubertal). 18/25 (72%) males were affected, 11/17 prepubertal, 7/8 pubertal/post pubertal. In females, both FSH and LH levels began rising 6 months post-BMT at 11.7±3.6 years reaching a peak of 58.1±52.6 (1–155) and 26.7±21.8 (0.1–68.2). In males FSH elevation began 3 years post-BMT at 14.2 (10.1–19.4) years to a peak of 22 IU/l (0.3–76.9); LH rose after 5 years at 16.9 (14.8–19.8) years to reach 24.3 IU/l (20.2–32.4) All 15 females but only five males required HRT aged 15.7±2.5 (12–20.8) years.

Conclusion
There is a high prevalence of PGF in paediatric ALL requiring BMT. The increased risk in all females and in pubertal/postpubertal males may be explained by limited follicular reserve in girls and increased Sertoli/Leydig cell vulnerability in older boys.

P41

Vitamin D deficiency in young survivors of childhood cancer

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Introduction
Childhood cancer survivors (CCS) are at risk of vitamin D (VitD) deficiency because of chronic ill health and advice to limit sunlight exposure. Studies have demonstrated associations between VitD deficiency and cardiovascular disease. Some CCS has increased risk of cardiovascular morbidity, but data on VitD status are limited.
Aim
To evaluate VitD status in CCS.
Method
We compared VitD levels in CCS ($n=83$ (M=42)) with controls of non-oncological endocrine patients ($n=232$ (M=112)). CCS included patients with solid cancers (SC; $n=43$) and haematological malignancies (HM; $n=40$) of whom 28 received BMT and 22 total body irradiation (TBI). Total 25-hydroxylase-VitD levels <25, <50 and 50–75 mmol/l were defined as severely deficient, deficient and suboptimal respectively. Patients with primary bone disease, malabsorption or VitD supplementation were excluded.
Results
(Mean $\pm$ S.D.) unless stated. There were no differences in the season of testing, gender, weight, height, or BMI-standard-deviation-scores (SDS) between the CCS and controls. CCS were older (14.7 (5.1) vs 10.3 (5.0) years, $P<0.001$), with more caucasians (92.8 vs 80.2%, $P=0.008$). Weight-SDS was lower in HM (-0.746 (2.05)) than SC (0.486 (1.72), $P=0.003$) or controls(-0.001 (2.01), $P=0.03$). VitD deficiency was more common (53 vs 48%) and levels lower (geometric mean (GM)=44.3 vs 48.6 mmol/l) in CCS compared with controls although not statistically significant. Sub-analysis demonstrated significantly lower VitD levels in HM compared with controls (GM=38.4 vs 48.6 mmol/l, $P=0.003$). This remained significant after correcting for age and weight-SDS ($P=0.004$). HM had significantly higher incidence of VitD levels below suboptimal (92.8 vs 79.3%, $P=0.037$) and more BMT patients had severe deficiency (25 vs 11.2%, $P=0.038$) compared with controls. VitD deficiency was more common in TBI patients after excluding non-Caucasians (65 vs 41.4%, $P=0.043$). Age correlated negatively with VitD levels in SC($r=-0.349$, $P<0.05$) and controls ($r=-0.225$, $P<0.001$), but not HM. Weight, height and BMI-SDS correlated negatively with VitD levels in controls, but not CCS. VitD deficiency was more common in winter months and non-Caucasians in all groups ($P<0.05$).
Conclusion
VitD deficiency is common in CCS, particularly HM. With its potential impact on cardiovascular health, VitD screening should be undertaken and supplementation actively considered as advice to minimise sunlight exposure is standard in CCS.

P42

Bone density in children with acute lymphoblastic leukaemia at a regional centre and comparison to children at risk of low bone density

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Introduction
Improved survival in childhood acute lymphoblastic leukaemia (ALL) has highlighted the importance of recognising and preventing skeletal morbidity. This study aims to assess bone health of ALL patients and compare this to other paediatric patients with chronic illness.
Methods
Dual energy absorptiometry (DXA) scan results for total body bone mineral density (TBBMD), lumbar spine bone mineral apparent density (LSBMAD) and total body less head (TBLH) were analysed for ALL patients referred between October 2008–August 2010. These were compared to scans from 141 children taken between May 2009–2010 and divided into nine subgroups by chronic disease. Bone profiles were reviewed if available.
Results
Patients with ALL made up 22 (13%) of total scans ($n=163$) with an age range of 4.8–17.8 years (92 males). 36% of the leukaemia patients ($n=22$) were referred following fractures. Of the ten comparison groups, patients with ALL had the second lowest mean (S.D.) TBBMD *Z*-score (-1.74, (1.54)), behind patients with metabolic pathway disorders (-1.86 (1.39)). ALL patients had the third lowest mean TBLH (-1.57 (1.49)), behind patients with metabolic pathway disorders (-2.02 (1.84)) and neurological conditions (-1.94 (1.02)), and third lowest LSBMAD (-1.43 (1.41)), behind patients with metabolic pathway disease (-1.88 S.D. 2.69) and bone disease (-1.64 (1.75)). Where results were available, 81% of patients with ALL ($n=16$) had vitamin D levels that were deficient or depleted (vitamin D ≤ 60 nmol/l).
Conclusion
Skeletal morbidity is likely to be multifactorial in patients with ALL and low bone density is evident when they are compared to patient groups with other chronic diseases, thus highlighting the need for a prospective observational study of bone health in this patient group.

P43

Chemotherapy treatment for medulloblastoma is associated with increased risk of impaired gonadal function

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Introduction
Effects on fertility have been seen as important late effects of treatment for childhood cancer.
Aim
To evaluate the impact of chemotherapy and radiotherapy treatment for childhood medulloblastoma on gonadal function.
Methods
Retrospective cohort study of all children treated for medulloblastoma (diagnosed from 2–18 years) in a single institution in the UK between 1983–2011 and a minimum relapse-free survival of two years. Data were obtained from medical records, including treatment and assessment of gonadal function (history, examination and biochemical assessment).
Results
Twenty four children treated for medulloblastoma between 1983 and 2011, with >2 years EFS (event free survival) were identified through a clinic database. Information was available on 20 patients (males $n=12$), median age 8.3 (range 2.4–13.4) years and disease free survival 14.3 (range 5.7–24) years. Treatment involved craniospinal irradiation (CSI; dose 32.5 Gy, 24–35 Gy) for all patients ($n=20$). Thirteen of these patients received additional chemotherapy (CT) including CCNU (doses 505 mg/m^2, range 150–720), the majority of them following the 'PACKER' protocol.
Of the 20 survivors 10 (50%) had impaired gonadal function. Three (15%) had hypogonadotrophic hypogonadism (HH). Seven patients (35%) had primary gonadal impairment (males $n=3$), all of which had received CT and CSI.
Of the 13 patients treated with CT and CSI, 54% (7) had primary gonadal impairment. No patients treated with CSI alone, developed primary gonadal impairment.
Discussion
The results show that 54% of children treated for medulloblastoma with CT and CSI have developed primary gonadal impairment. Primary gonadal impairment was not seen following CSI alone, although HH is widely recognized.
Long-term follow up in patients who received CT for medulloblastoma is therefore necessary to monitor their gonadal function. Fertility preservation, where possible, should be considered in patients receiving CT for medulloblastoma.

P44

The use of continuous s.c. insulin infusion therapy to optimize glycaemic control in children with type 1 diabetes mellitus

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Aim
To investigate the glycaemic control of patients with T1DM before and after the introduction of CSII therapy.

Methods
All patients with T1DM receiving CSII therapy for more than 6 months attending the Children's University Hospital from 2005–2011 were included. Glycosylated haemoglobin (HbA1c) was recorded 12 and 6 months prior to starting therapy, at the time of CSII initiation and annually thereafter. Adverse events and BMI were also recorded at these intervals.
Results
Data was collected on 104 children (52 males). The mean age at diagnosis of T1DM was 6.4 years (range 0.7–15.4 years). CSII therapy was commenced at a mean age of 10.3 years (range 0.9–17.3 years) with a mean duration of therapy of 2.5 years (range 0.5–5.9 years). Mean (S.D.) HbA1c pre CSII therapy was 8.6% (1.0) with values of 8.1% (0.87) 1 year after commencing therapy ($P<0.05$). The HbA1c value at 2–5 years after commencing pump therapy were 8.2% (0.79), 8.1% (0.78), 8.1% (0.68) and 7.9% (0.37) respectively ($P<0.05$). There were three adverse events (diabetic ketoacidosis, severe hypoglycaemia) per year prior to CSII therapy and 1.2 events per year after its initiation. No change was seen in BMI *Z* score pre and post CSII therapy. No site infections were seen.
Conclusion
Tight metabolic control reduces the incidence of micro vascular complications in T1DM (DCCT Research Group J Pediatr 1994). In this study, HbA1c improved significantly following introduction of CSII therapy and this improvement was maintained over the study period. CSII therapy is a safe and effective method to optimize and maintain glycaemic control in children with T1DM.

P45

Uptake of BSPED revised guidelines for paediatric DKA management in Scotland

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Introduction
Diabetic ketoacidosis remains the leading cause of morbidity and mortality in children with type 1 diabetes. BSPED guidelines for management of paediatric DKA were revised in 2009.
Methods
We performed a telephone questionnaire of all 13 centres in Scotland who provide inpatient paediatric (<16 years) care, and reviewed their DKA guidelines. These were audited against the 2009 BSPED guidelines. Criteria studied were; method of ketone measurement; maximum percentage of dehydration; maintenance fluids; minimum time on isotonic fluids; commencement of insulin; long acting analogues; end point of DKA management; treatment of cerebral oedema.
Results
Overall, there was 38.5% compliance with BSPED guidelines for these criteria. Eight of 13 centres use blood ketone measurement. Nine of 13 centres use 10% as the maximum dehydration calculated for DKA, three centres use a maximum of 8%. Maintenance fluids are calculated using the BSPED calculation in three centres, and the ISPAD calculation in five centres. Three centres state minimum time on isotonic fluids of 12 h, four state 4–6 h. Nine of 13 centres delay commencing IV insulin until 1–2 h after fluid replacement. Ten of 13 centres use BSPED initial doses of insulin, two centres use lower starting doses. Four of 13 centres continue subcutaneous glargine during treatment for DKA. Six of 13 centres use blood ketones as an endpoint of DKA treatment, four centres use a clinical end point. Six of 13 centres recommend hypertonic saline or mannitol as first line for treatment of cerebral oedema.
Conclusion
The changes suggested in the BSPED guidelines have been taken up 38.5% of instances. Improved education is necessary to ensure that all children with DKA receive optimum care. Outcome data is also needed following changes.

P46

The use of glucose meter downloads in monitoring childhood diabetes mellitus

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Aims
The use of glucose meter downloads provides statistics (mean blood glucose level, S.D.) which may have a role in outpatient Diabetes monitoring. We aimed to compare these measures with the current gold standard, HbA1c.
Methods
Thirty-eight patients had blood glucose readings downloaded from their monitoring device (*Accuchek)* at clinic visits over 25 months. Statistical analysis from the *Accuchek* Software package was performed to produce a data report including the following parameters: number of glucose readings, test frequency, mean blood glucose, S.D of glucose readings. The HbA1c was also recorded for each clinic visit and used for comparison to the download parameters. Reports with a test frequency of <2/day were excluded from analysis.
Results
115 downloads were obtained. Number of recorded glucose levels per download report had a range of 69–500 readings (frequency 2.0–6.0/day, mean 3.6). HbA1c levels had a median 9.9 (range 6.8–14). S.D of glucose readings correlated significantly with an increased HbA1c value (regression coefficient of 0.54, $P<0.0001$, 95% CI 0.39, 0.68). A significant positive correlation was also found between mean blood glucose and HbA1c values (regression coefficient of 0.91, $P<0.0001$, 95% CI 0.60, 1.22). Mean blood glucose level also correlates well with S.D of readings (regression coefficient 1.2, $P<0.0001$, 95% CI 0.84, 1.56). Outliers included a girl with leukaemia and two patients with extended 'honeymoon periods'.
Conclusions
Parameters such as mean blood glucose and S.D correlate very well with HbA1c despite lack of control over frequency/timing of measurements. However, the other parameters used in this study may be useful adjuncts in recognising patients with unusual diabetes control patterns (outliers) who require closer investigation as to why this may be occurring.

P47

Audit of paediatric patients with IDDM on CSII (pump) therapy in a District General Hospital

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Introduction
Continuous subcutaneous insulin infusion (CSII) or 'pump', therapy is used for intensification of insulin therapy. NICE guideline 2008 recommends CSII as an option for adults / children 12 years or older with insulin dependent diabetes mellitus (IDDM), when multiple daily injection (MDI) insulin therapy results in disabling hypoglycaemia/fails to reduce HbA1c levels below 8.5%, and for children below 12 years whenever MDI is impractical or inappropriate. Nevertheless, the cost implications are high in terms of equipment and time. This retrospective audit looks into the effectiveness of pump service in a DGH and compliance with NICE guidance.
Methods
Children 0–16 years with IDDM on CSII attending paediatric diabetes service in Singleton Hospital (2007–2011) were identified. Data were collected from the diabetes database, notes and pathology system.
Results
Of the 165 children with IDDM attending our service, 30 patients were on CSII during this period. (one lost pump). 24/29 patients improved their HbA1c (mean difference, 1.5%; best, 5.1%). Mean HbA1c of the group pre pump was 9.28% and post pump was 8.05%, with mean improvement of 1.2%, $P<0.0001$ (95% CI 0.64–1.754). Mean HbA1c of the non pump patients was 9.03% ($P=0.0089$; 95% CI 0.258–1.762). 14/29 patients had improvement of hypoglycaemia (moderate/severe). Hyperglycaemia admissions to hospital were 81%. We identified 2–3 patients who were not quite meeting the HbA1c outcome targets and few patients over 12 years have had pump holidays.
Conclusions
There was a significant improvement in HbA1c with CSII therapy. It was not possible to quantify a 'quality of life' improvement in this audit. As a service development, we aim to develop a virtual pump clinic.

P48

The lived experiences of children and parents using continuous s.c. insulin infusion or insulin pump

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Background
Type 1 diabetes mellitus is increasing in children (ISPAD 2009). Tight metabolic control using intensive insulin therapy aims to reduce short and long term complications. Continuous subcutaneous insulin infusions (CSII or pump therapy) as a method of insulin delivery has resulted in improved glycaemic control (Danne & Tambourlane (2006) and Onwuneme & Devenney (2009).

However there is little evidence of the impact of pumps on the lived experience of children and parents who use insulin pumps.
Aims and objectives
The aim of this research was to investigate and describe the lived experiences of children and parents who use an insulin pump.
Methods
A qualitative approach was used which is grounded in phenomenology, which is rich in detail and opens possibility of understanding. All children and parents who have been using an insulin pump for at least 3 months were invited to participate in a focus group. The focus group took place on a Saturday morning. There were separate focus groups for children and parents and the children's focus groups were age banded. The focus groups were audio taped and the facilitator was not a member of the diabetes team.
Analysis and results
Nine children (six children aged 6–12 and three over 12) and ten parents (six parents of children aged 6–12 and four parents of children over 12). The audio tapes were transcribed and analysed using Colaizzi's framework (1978). Emerging themes for children included 'normal; freedom' with food, playing and time and 'flexibility', with food and times. Emerging themes for parents also included 'normal; freedom; flexibility'; and 'trust'. Rigour was established by credibility, dependability, and confirmability.
Conclusions
Insulin pumps were universally preferred and offer freedom and flexibility. All children have elected to continue using pumps. The lived experience of children and parents using an insulin pump is positive and favoured over insulin injections

P49

Frequency of blood glucose testing correlates poorly with HbA1c values in children with type 1 diabetes mellitus

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Aims
The use of glucose meter downloads in outpatients enables clinicians to monitor how frequently children with type 1 diabetes mellitus are testing their blood glucose level on a daily basis. We tested the hypothesis that increased frequency of blood glucose testing improves HbA1c value, the current gold standard in monitoring diabetic control.
Methods
Thirty-eight patients had their glucose meter (*Accuchek*) downloaded at outpatient clinic visits over a 25-month period. The *Accuchek* download package was used to give values for number of blood glucose readings and a daily frequency value (number of tests per day). HbA1c values were also measured at clinic visits and comparison made with test frequency. Sub-group analysis was performed using insulin regime as a parameter. Regimes were divided according to frequency of insulin administration (twice daily, three times daily, basal bolus or pump regimes).
Results
115 downloads were obtained. Test frequency for the whole cohort had a range of 2.0–6.0/day (mean 3.6). HbA1c levels had a range of 6.8–14 (median 9.9). There was only very poor correlation of test frequency with HbA1c (regression coefficient 0.04) and this had low power of significance ($P=0.03$, 95% CI -0.02, -0.33). There was no difference in correlation found on sub-group analysis according to insulin regime (regression coefficients range -0.19 to -0.28).
Conclusions
Increasing frequency of testing blood glucose level does not correlate well with any improvement in HbA1c level. This holds true for children on any of four different groups of insulin dosing regimes. Other techniques are more likely to be effective in improving HbA1c values than solely increasing the frequency of glucose testing in children.

P50

Using self-monitoring of blood glucose to improve understanding and self-management of diabetes in children and young people with type 1 diabetes in a routine clinical setting

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Introduction
The strong correlation between HbA1c and blood glucose (BG) has been recognised in many studies. We investigated this relationship using BG data from 119 children with diabetes, to better understand factors affecting HbA1c and characteristics of children with good versus poor control.
Methods
BG data was obtained on 119 children over a 1-month period and on a subset of 43 children over three consecutive months using the Diasend System (Aidera, Sweden). HbA1c was obtained at the beginning and end of the 3-month period. Linear regression was used to assess the relationship between HbA1c and BG and any additional effects of BG variability or age.
Results
Our model confirmed the linear relationship between HbA1c and BG. Each additional 1 mmol BG corresponded to an increase of 0.35 (95% CI 0.3–0.4) HbA1c%. Age had a significant effect on HbA1c after adjusting for average BG ($P=0.003$) – for an average BG of 10 mmol, predicted HbA1c measurements were 7.8% for age eight and 8.1% for age fifteen. The 3-month data showed a significant relationship ($P=0.027$) between absolute change in HbA1c and BG variability (S.D.). Children with more variable BG were more likely to have a larger change in HbA1c. Children with poor control (HbA1c $>9.5\%$) tended to take fewer BG measurements, have more variable measurements, and have a peak measurement between 1800–2000 h compared with those with good control ($<7.5\%$).
Conclusion
Routinely downloading BG meter readings has been well accepted by parents and children and has become an essential part of clinical consultation. It allows HbA1c to be expressed as the more easily understood average BG, enables children to visualise and discuss their data, and identifies areas in which to target improvements. We recommend that downloads and assessment of average BG becomes routine in clinic.

P51

Continuing variation in DKA guidelines despite national guidelines

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Since the introduction of national BSPED DKA guidelines we wondered whether the previous variability in DKA guidelines would be abolished.
Aim
To explore the variability of guidelines in three regional diabetes networks in South West (SW) and South Central England and to compare them to the current BSPED guidelines.
Methods
Within an audit of in-patient care, a copy of the DKA guidelines was requested from 27 services. General layout, fluid and insulin, potassium and bicarbonate recommendations and cerebral oedema (CO) management were analysed.
Results
Thirteen guidelines were obtained from 20 centres (seven centres in SW use the same integrated care pathway). Three were between 5 and 7 years out-of-date. For shock, all suggested 0.9% NaCl, with an initial 10 ml/kg fluid bolus in 10 guidelines and a maximum 30 ml/kg in nine. All stated a maximum degree of dehydration; one used 7.5%, five used 8% (new BSPED maximum), and seven used 10%. The rehydration period varied; 48 h in 11, 24–36 h in one and 36 h in one. A standard calculation was done of a 6-year-old child weighing 20 kg, maximally dehydrated; the variation in initial fluid replacement was substantial, between 75 and 137 ml/h. 0.9% NaCl with KCl was continued for 12 h in five guidelines. Eight suggested delaying insulin for an hour after IV fluids. Insulin infusion rate started at 0.1 units/kg per h in 11 guidelines. Five guidelines clearly instructed maintaining the insulin infusion rate when BG fell to 14 mmol/l. CO was mentioned as an important cause of morbidity in all guidelines. All suggested either mannitol or hypertonic saline and to reduce fluid rate to 2/3 or 1/2 maintenance rate.
Conclusion
In spite of availability of national and international guidelines, a large degree of variation still exists in many aspects of management. In particular, variation in fluid calculations remains a concern, given that fluid volume is a risk factor for CO.

P52

Educating children in continuous subcutaneous insulin infusion (CSII) therapy; are we improving diabetes control?

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Background
Continuous subcutaneous insulin infusion (CSII) is proving superior in reducing HbA1c compared to multiple daily injections (MDI) in both the adult and paediatric populations. This study aims to compare the two methods, and evaluate the importance of education when starting insulin pump therapy in children.
Design
Patients who attended a 'pump school' provided by the Royal Manchester Children's Hospital between January 2010 and 2011 were included in the study. Five key aspects of diabetes control were assessed for a year before and a year after starting on CSII. Pump school was compared against current NICE recommendations for education and patient voice was gained through user satisfaction surveys.
Results
Twenty patients attended pump school, with 17 going on to CSII long term. The median age at starting pump therapy was 10 years (IQR 8.5–12). Fourteen patients were on MDI prior to CSII, three were on twice daily injections and all but one attended group education sessions at the hospital.
Average HbA1c decreased by 0.85% (s.d. 0.8) after starting pump therapy ($P<0.001$). CSII also decreased the number and severity of episodes of hypoglycaemia ($P<0.04$) and increased quality of life with 100% of patients strongly agreeing that it increases flexibility in diet. Pump school follows closely NICE recommendations, and all patients feel confident to use a pump when leaving the school; however 30% of patients felt that the number of sessions could be condensed. 63% of patients felt a yearly revision session would be beneficial, and this should combat an increase in HbA1c after the initial drop.
Conclusion
Pump therapy is successful in decreasing HbA1c and hypoglycaemic episodes in comparison to MDI. Thorough training is provided when NICE guidelines are followed, however a review of number of sessions as well as a yearly revision session should be considered.

P53

An unusual case of type 1 diabetes mellitus and autoimmune limbic encephalitis

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Introduction
T1DM is an autoimmune condition. At diagnosis, 80% of patients have positive glutamic-acid decarboxylase antibodies (GADA). We report a case of T1DM diagnosed 1 year after the onset of autoimmune limbic encephalitis (LE).
Case
A 13-year-old female was diagnosed with voltage-gated-potassium channel (VGKC) positive LE after presenting with complex partial seizures and auditory hallucinations. A year later and prior to the diagnosis of diabetes her neurological condition deteriorated with worsening of axial stiffness, escalation of seizure frequency, short memory deterioration, hallucinations and emotional lability. At the time of a PET scan to exclude neoplasia, the patient was found to have hyperglycaemia. Her HBA1C was 7.1% and high levels of GADA were detected (>2000 U/ml). There was evidence of acanthosis nigricans and a strong family history of type 2 diabetes. She was initiated on subcutaneous insulin with multiple daily injections. She received intravenous corticosteroids, plasmapharesis, mycophenolate mofetil and intravenous immunoglobulin as part of her neurology management which complicated the management of her diabetes. Her total daily insulin dose varied between 0.5 and 2.0 units/kg per day depending on her fluctuating neurological status.
Conclusion
Neurological conditions with GADA have been described in adults and diabetes may pre-exist or manifest after the onset of the neurological symptoms. LE is associated with antibodies such as VGKC-antibodies and GADA and has been most commonly described as a paraneoplastic phenomenon. To date, 16 children with LE have been reported (six paraneoplastic); five were GADA positive; one was diagnosed with T1DM 2 years prior to the onset of LE. Our patient developed T1DM 1 year after the onset of LE and her glycaemic control was complicated by her fluctuating insulin sensitivity, her underlying neurological condition and its management.

P54

Confounding factors and variations in HbA1c collection methods have not shown different HbA1c results as compared to the National Paediatric Diabetes Audit Results

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The National Diabetes Paediatric Audit Report (NDPAR) 2009–10 was published earlier this year. A total of 155 units submitted data to the report, representing an overall increase of 31 units since the 2008–9 audit. Whilst non-participation has been largely attributed to lack of resources and technical infrastructure, there are some concerns over the method of data collection and interpretation.
Our unit entered the data by using the automatic extraction function of the Twinkle database. With this method only the latest single HbA1c entrance is used which gave our unit a median value of 9.1% (range = 6.0–15.0%, $n=214$). We reviewed the data of the same 235 patients that we submitted to the 2009–10 NDPAR and used different criteria to analyse the HbA1c. We hypothesised that audit results could be confounded by not taking an average HbA1C per patient over the whole audit period, the HbA1c within 6 or 12 months of diagnosis as well as patients that came to us from out of area with difficult to manage diabetes.
In our analysis we calculated the mean HbA1c value for each patient over the whole period giving a median of 9.13% ($n=216$), representing no difference to the NDPAR.
With regards to patients with newly diagnosed diabetes during the audit period, exclusion gave a median of 9.13% ($n=195$). When we excluded new diagnoses up to a year before the audit period we found a median of 9.23% ($n=174$), showing a slight increase of the median.
Finally, we excluded the patients that were from out of area which resulted in a median of 9.13% ($n=207$).
Excluding both new diagnoses up to a year before the audit period and our out of area patients resulted in an unexpected increase of the median to 9.25% ($n=165$).
Overall the results of our review show no, or only minimal, differences in HbA1c values for the different confounding factors as compared to the NDPAR, suggesting that the current data collection is a valid method.

P55

A case of non ketotic hyperglycaemic hyperosmolar coma in a child precipitated by pancreatitis

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Introduction
Non-ketotic hyperglycaemic hyperosmolar (HHNK) coma is rare in children, is associated with high mortality rate. The incidence of this condition is reported to be increasing and considered to be related to increased prevalence in obesity and type 2 diabetes in children. Hyperglycaemic hyperosmolar syndrome (HHS) is rare in children. The pathophysiology and management of HHS is a distinct entity from diabetic ketoacidosis (DKA).
Case report
We report a case of HHNK coma in a 4-year-old African boy who presented with severe dehydration (pH-6.8, base deficit-27.1, lactate 13.7), non-ketotic hyperglycaemia (blood glucose 49.7 mmol/l), hyperosmolality (400 mOsm/l) and serum sodium of 163 mmol/l. On admission he presented in coma (GCS 3/15) and shock, requiring intensive resuscitation with airway support, fluids (40 ml/kg of fluid boluses) and inotropic support. He was noted to have abdominal distension with a serum amylase of 188 IU/l (normal 30–110). With meticulous attention to vigorous initial fluid replacement (10% deficit + maintenance 0.9% saline followed by 0.45% saline) as opposed to over 48 h in DKA and low dose insulin infusion (0.025 IU/kg per h), there was a sustained correction of the hyperglycaemia over 4 days.
His BMI was 16.2-kg/m^2 -nonobese, with no acanthosis nigricans, no insulin antibodies but with an elevated insulin level (>100 mIU/l). No family history was available as he was adopted from Uganda. Currently he is in good health with no insulin requirement.

Conclusion
This is a rare case of HHS in childhood, which demonstrates that the use of low dose insulin infusion and strict attention to fluid replacement mitigates against co-morbidity. The learning point: one should always suspect HHS in a child presenting with hyperosmolar hyperglycaemia without ketosis and that pursuing standard management for diabetic ketoacidosis is not indicated.

P56

Pigmented hypertrichosis and insulin dependent diabetes mellitus (PHID) syndrome is associated with chronic inflammation and involves the NF-kB response pathway of inflammation

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Background
Pigmented hypertrichotic dermatosis with insulin-dependent diabetes (PHID) syndrome is an autosomal recessive disorder due mutations in *SLC29A3*. *SLC29A3* encodes for an equilibrative nucleoside transporter 3 (ENT 3). A hallmark of PHID syndrome is the chronic inflammation characterised by the persistently raised erythrocyte sedimentation rate and C-reactive protein. A key pathway involved in triggering inflammation is the nuclear factor kappa β (NF-kB) pathway. NF-kB is a transcription factor which when activated will trigger a host of genes involved in regulating the inflammatory response. Thus activation and modulation NF-kB pathway is central to the inflammatory pathway. The mechanism/s underlying the chronic inflammatory response in patients with PHID is/are not known.
Aims
To understand the molecular basis of the inflammatory response in PHID syndrome.
Methods
Serum amyloid A protein levels were measured patients with PHID syndrome. The expression of *SLC29A3* was knocked down in HeLa cells using *SLC29A3* specific shRNA constructs in GIP Lentiviral plasmids (Open Biosystems, Huntsville USA) and the inflammatory response to *SLC29A3* knockdown was interrogated using a construct with tandem NF-kB response elements driving Luciferase (pGL4.32[luc2P/NF-κB-RE] Promega).
Results
Serum amyloid A protein levels were markedly elevated (60–90 mg/dl ref <10). Our preliminary data indicate that knock-down of *SLC29A3* expression alters the inflammatory response mediated by NF-kB response.
Conclusion
The inflammatory response in PHID patients is associated with the accumulation of serum amyloid A protein and our preliminary data indicate that the transcription factor NF-kB may be involved in the inflammatory cascade. Further studies are required to understand the link between nucleoside transport and the inflammatory response in patients with PHID syndrome.

P57

Quality of life in children with type 1 diabetes in Kuwait

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Introduction
Recent research has shown that health-related quality of life (HRQOL) in children and adolescents with type 1 diabetes is markedly affected, resembling that of children with other chronic diseases, like malignancies. The objective of the study was to investigate the HRQOL in children and adolescents with diabetes in Kuwait.
Method
A total of 341 children and adolescents aged 5–18 years and 408 parents of children aged 2–18 years participated in the study. They were recruited from diabetes out-patient clinics in the six governorate hospitals. The pediatric quality of life inventory (PedsQL) questionnaire was used.
Results
The mean ($\pm$S.D.) age of participants was 9 ± 1.2 years, and the duration of diabetes was 4.9 ± 2 years. The Cronbach a coefficient of child and parent report generally approached 0.825, indicating their internal consistency and reliability. There was a statistically significant difference in the total scores among children and their parents in all three age groups ($P<0.001$), however, to a lower degree in the adolescent group, where the main difference was in the 'worry' section where parents reported worse QOL. The total scores showed good psychological adjustment of children and adolescents with diabetes, mean score ($\pm$S.D._ was 85.7 (12.45), with slightly worse QOL in the 8–12 year old (71.2 ± 13.1) $P>0.05$. Growing age, HbA1c, mode of insulin therapy, SES did not influence QOL of children with diabetes.
Conclusion
Children and adolescents with type 1 diabetes and their parents in Kuwait showed good psychological adjustment and QOL. Parents appeared to be more worried than their adolescents about the effectiveness of the treatment and the long term complications.

P58

Effect of diagnosing coeliac disease and instituting a gluten-free-diet on glycaemic control in asymptomatic children with type 1 diabetes mellitus

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Background
Coeliac disease (CD) is common in children with type 1 diabetes mellitus, so that CD screening of all asymptomatic diabetic children is carried out in many medical centres. While introduction of a gluten-free diet (GFD) might improve glycaemic control, the burden of two dietary regimes could adversely affect compliance.
Aim
To assess the short-term effect of the diagnosis and treatment of asymptomatic CD detected by screening on diabetic control and anthropometric measurements 1 year before and 1 year after the diagnosis of CD and introduction of GFD in children with type 1 diabetes at a single paediatric centre.
Design
Retrospective longitudinal case–control study of 21 diabetic children with CD and 21 diabetic controls matched for age, sex, and duration of diabetes.
Results
In 21 pairs (24 girls, 18 boys), the age at diagnosis of diabetes mellitus in coeliac group and controls was 5.6 ± 3.3 and 5.8 ± 3.2 years, respectively ($P=0.8$). The coeliac cases were diagnosed with CD at 11.1 ± 2.45 years of age. HbA1c levels (%) were 8.49 ± 1.35, 8.35 ± 1.17, and 8.45 ± 0.99 in controls, coeliac cases pre-GFD, and post-GFD, respectively. HbA1c, insulin requirements, height SDS, weight SDS, BMI SDS did not change in coeliac cases 1 year before and after of introduction of GFD. All of these values during pre-GFD and after-GFD periods were similar to those of controls with exception of insulin requirement, which was significantly higher after diagnosis of CD than in controls (1.28 ± 0.36 vs 1.09 ± 0.38 unit/kg per day, $P=0.001$). Individual analysis of all values at each time point between cases and controls did not reach statistical significance over the 2-year period.
Conclusion
We have found no evidence that diagnosis of CD and introduction of GFD in diabetic children affects glycaemic control or growth. However, it may be associated with a slight increase in daily insulin requirements.

P59

Permanent neonatal diabetes mellitus due to a homozygous R397L (Glucokinase) mutation managed with CSII therapy

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Introduction
Neonatal diabetes mellitus is a rare condition with an estimated incidence of 1 in 400 000 live births in the UK population. Half of these cases will have permanent

neonatal diabetes mellitus (PNDM). We report a homozygous missense mutation (R397L) in the glucokinase (*GCK*) gene which is associated with PNDM, in an infant from a consanguineous Asian family.

Case report

The baby was born with a birth weight of 1.68 kg at 38 weeks gestation and presented with severe hyperglycaemia without ketosis from day 2 of life. Mother was diagnosed with gestational diabetes in her second pregnancy and has been on metformin since but she was treated with insulin during this (her 4th) pregnancy. The baby initially required an intravenous insulin sliding scale (insulin requirement 1 unit/kg per day) and at 4 weeks of age commenced on a continuous subcutaneous insulin infusion (CSII). The basal insulin rate was started at 0.025 units/h and was gradually increased up to 0.1 units/h (total daily dose 1 unit/kg per day). Bolus insulin doses of 0.1 units were given for 100 ml feeds with additional correction doses of insulin between 0.1 to 0.2 units depending on her pre feed blood glucose concentration. The insertion of subcutaneous cannula for insulin pump was a challenge due to her age and the lack of subcutaneous tissue. Stool elastase was normal excluding pancreatic agenesis. Gene sequencing identified a homozygous mutation, R397L, in the *GCK* gene which confirmed a diagnosis of PNDM.

Conclusion

The management of neonatal diabetes in challenging not least because of the associated IUGR. Although CSII therapy is likely to provide the best glucose control it is technically difficult. To date, five reported cases of PNDM have been shown to be due to homozygous or compound heterozygous inactivating mutations in the glucokinase (*GCK*) gene. In the heterozygous form, *GCK* mutations cause maturity-onset diabetes of the young (GCK-MODY). We concur with the policy of central genetic testing for these patients and suggest that CSII is the therapeutic intervention of choice.

P60

Reducing the risk of serious infections for children with diabetes mellitus: an audit of immunisation practice

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Introduction

Patients with diabetes mellitus are known to have increased mortality and morbidity from influenza and pneumococcal disease. The Department of Health recommends that these children, along with other high risk patients, receive yearly influenza vaccination and additional immunisations against invasive pneumococcal disease. We audited the uptake of these additional immunisations in our patients.

Method

Retrospective audit of all patients with type 1 diabetes under the paediatric diabetes team at our district general hospital in June 2011.

Patients younger than 2 years old or diagnosed within the last year were excluded. Vaccination history was obtained from their general practitioners.

Results

Vaccination records were available for 84 patients. Eleven were excluded due to diagnosis within the last year. One patient had a concomitant risk factor of cystic fibrosis. 46% of patients were male, median age 14 years (IQR 10–16). Patients were distributed across 26 general practices.

Forty-two patients (57%) had been vaccinated against influenza in the preceding 'flu season. 13 patients (18%) had never received an influenza vaccination.

Nineteen children (26%) received at least one vaccine against pneumococcal disease, of whom three received routine pneumococcal conjugate vaccinations but not the additional polysaccharide vaccine, and 17 received appropriate pneumococcal polysaccharide vaccinations. In total, 17 children (23%) were appropriately immunised against pneumococcal disease.

Overall, 15 patients (21%) with DM were appropriately vaccinated against both influenza and pneumococcal disease.

Conclusion

The vast majority of our patients are inadequately vaccinated against influenza and pneumococcal disease. Rates of pneumococcal immunisation are substantially lower than those of influenza. This may be due to increased public awareness following the recent influenza pandemic.

Vaccine coverage in these high risk patients needs to be improved. This will require increased awareness of the immunisation requirements of children with diabetes within primary care, supported by specialist paediatric diabetes teams.

P61

Young people have a limited knowledge about diabetes research

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Individuals considering research participation are provided with information but this is usually at the end of the process of engagement. Getting young people interested in research can be difficult, even more so when competing against a demanding school and social life that many young people lead. Working with a group of young people we produced a pilot website containing video and text material about diabetes and research that was designed to be appealing and informative.

We used qualitative methods to assess the success of the material. A focus group of young people gave feedback firstly on their awareness of research and secondly on the website and video material. We chose a focus group to evaluate our research because this method has been used successfully to access hard-to-reach populations, such as young people. Five young people, three with diabetes two without diabetes aged 18–20 years volunteered to take part in the group.

All of the participants felt unaware of the wide variety of research being undertaken and the term research was clearly linked to laboratory research and this it was felt would put young people off. The material was received well by the group and had a positive impact on their perception of research and made them more open to volunteering for research. They also identified that taking part in research has an altruistic side, in helping others, but also a personal benefit in understanding their condition. Furthermore the participants felt the material had perhaps missed the relevant age group and would be more appealing to younger teenagers 13–15 years old.

Focus groups offer a useful and informative way to assess patient materials. Data from this pilot project indicate that there is limited knowledge about research and that better understanding could lead to increased participation.

P62

Care of newly diagnosed children with diabetes: survey of general practitioners

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In the UK, over 95% of children age 0–16 years presenting with diabetes have type 1 diabetes. Up to 25% of these present with DKA. Many present initially to GPs and it is important that children with symptoms of diabetes are referred urgently to Paediatric Diabetes Team.

Aim

We carried out a survey of the current practise of GP's when they suspect DM in a young person. The aim was to investigate whether they recognised the need for urgent referral to Paediatric Diabetes Team (PDT).

Method

Three hundred local GP's were asked to complete a Questionnaire indicating what actions they would take when faced with a well 11-year-old with typical symptoms of DM and point of care blood glucose was more than 11.1 mmol/l. Statistical analysis was made by MINITAB 15. χ^2 was used to examine factors that affected choices made by the GP's.

Results

37% (111/300) replied. Of these 34.5% would have taken an action that would have led to delay in both referral to PDT and delay in initiation of appropriate therapy. There were no statistical difference between those who had declared a special interest in adult DM or had been involved in the care of newly diagnosed child with DM in the actions they would take ($P=0.9$ and $P=0.84$ respectively). 23.6% of GP's felt that childhood DM should be managed by themselves in Primary care. This again had no relation as to whether they would have referred in a timely manner or not ($P=0.35$). A third of our local GP's actions would result in delayed referral and therefore risk of DKA. There is a need to increase awareness amongst GPs about need to act urgently when a child is suspected to have diabetes mellitus.

P63

Audit of structured educational programme for carbohydrate counting for children with type 1 diabetes

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Introduction
The paediatric diabetes team in Leicester identified an unmet need for educating children about carbohydrate counting, following the initiation of most diagnosed patients on multiple dose insulin therapy (MDI). The team therefore started a new structured group education programme (SGEP) for children with type 1 diabetes (T1DM) called flexible adjustment of basal bolus (FABB) that has run since January 2007.
Aims
To determine the effectiveness of SGEP for children with T1DM and to compare the outcomes of MDI therapy before (data from previous audit) and after introduction of SGEP.
Methods
This is a retrospective audit of children with T1DM who had SGEP over a period of 1 year (1 Jan–31 Dec 2008). Thirty-five case notes were identified and HbA1C, BMI and number of hypoglycaemic episodes (NHE) at baseline, 6 months, and 1 year were analysed.
Results
Mean HbA1C improved by 0.9% (9.5–8.6%) at 6 months 0.8% (9.5–8.7%) at 1 year, compared to pre FABB that didn't show improvement in HbA1C 9.1% at all the time points. Mean BMI was not significantly different between the time points (post FABB 19.6, 20.0, 20.6 kg/m^2, pre FABB 22,9,22.9,22.8 kg/m^2). Mean NHE didn't differ between time points in the post FABB group. However mean NHE was increased in the post FABB group compared to pre FABB at the final 1 year time point but not at baseline and 6 months. (0.028, 0.028, 0.033 vs. 0.02, 0.03, 0.00).
Conclusion
Since the introduction of our SGEP there was a sustained improvement in HBA1C by mean of 0.9 and 0.8% at 6 and 12 months compared to a group of children who were started on MDI that didn't receive SGEP. It did not change the outcomes of BMI and NHE at 6 months but increased at 1 year in post FABB group. However our mean HbA1C is higher than the NICE recommended standard of $<7.5\%$ and reaudit prospectively from 2011 is needed to assess if we are nearer to this target having run the SGEP for 4 years.

P64

Internet-based information resources for young patients and families with diabetes mellitus: a user preference survey

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Background
Internet-based education and information resources for young people and families with DM have increased, yet the extent of use and perceived value among this patient group is uncertain. We conducted a questionnaire-based survey of parents' and carers' experience of currently available DM internet-based resources.
Objective
To assess i) level of internet use, ii) perceived quality of patient support information currently available, iii) need for a local diabetes clinic website and iv) preferred website content.
Method
Questionnaire survey delivered to the carers of a random sample of children and young people with DM (age 0–18 years) attending a tertiary paediatric diabetes clinic (*n* 280). Quality and perceived value of internet-based information was rated from 1 (poor) to 5 (high).
Results
Seventy-four carers completed the questionnaire. 96% have home internet access, although only 76% used this to access information about DM. Topics most frequently searched were: equipment (blood glucose meters, pens and pumps (68%)), 'what is diabetes' (64%), carbohydrate counting (62%) and long-term complications (62%). Least searched for included how to give insulin (32%) and instructions about how to use kit (34%).
Information on 'what is diabetes' was rated highest in quality (mean (S.D.) = 4.5 (0.6)) whereas information relating to 'diabetes in school' (3.0 (1.3)) and 'support meetings and other events' (3.0 (1.3)) was rated lowest. 81 and 34% of users respectively found the Diabetes UK and JDRF websites useful. Overall users found information from external internet sites 'untrustworthy' (25%), 'distressing' (15%), 'too technical' (11%), 'inadequate (19%) or excessive (9%), with 71% preferring to receive information about DM from a 'trusted' local clinic website.
Conclusion
Internet use amongst young patients and families with DM is high. The quality of information is rated highly variable with the majority of users preferring to receive this from a trusted local website.

P65

Assessment of standards of care in children's diabetes services across Yorkshire and Humber SHA

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Background
A children's diabetes network was established in late 2008 across the Y&H SHA. Following agreement from all units over 2009/10 it identified outcome measures and established policies leading to 2011 being a 'Year of Action' to produce significant improvement in services.
Methods
All units were required to submit annually to the NDA and to complete an extended version of the 2008 Diabetes UK questionnaire on staffing. Data from the 2008/9 and 2009/10 NDA, together with the Staffing Survey and the established paediatric register were independently analysed by the Paediatric Epidemiology Unit University of Leeds. A resource score was developed based on recommended staffing levels.
Results
Details from 21 units and 2421 children with diabetes were collected. No unit achieved maximum resource score of 15 (mean 9.1 range 6.5–12). There was no significant difference in resources across units but outcomes varied significantly with the number of children with HbA1c $<7.5\%$ ranging from 3 to 30%.
HbA1c was adversely influenced by: i) age at diagnosis: with each additional year of age at diagnosis resulting in an increase of 0.01–0.02; ii) duration of diabetes: with each additional year resulting in a 0.12 increase and iii) deprivation: with a 0.78 increase from the least to most deprived in HbA1c.
Units with better outcomes and higher % of HbA1c $<7.5\%$ had better control from diagnosis and higher % on MDI/pumps although there was a wide range across units.
Conclusion
Although there is a significant issue of resource across all units, there was a wide variation in outcome between units. The Y&H SHA Project Board are embarking on a 'Peer review' programme to help units learn from each other and identify ways forward to improve diabetes services.

P66

Audit on psychology/psychotherapy support in children with diabetes

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Introduction
In the United Kingdom, the prevalence of type 1 diabetes in the under-15s is rising fast, an increase of 80% is expected by 2020 and even higher, 125%, in the under five age group. The National Service Framework Standard recommends that all children/young adults with diabetes should receive consistently high quality care and they, with their families, be supported to optimise the control of their blood glucose and all aspects of their subsequent development.
Aim
To assess young children/adolescents with diabetes who need psychology support in primary/secondary care. The services currently available involves hospital doctors, dietician and nurse specialist. To look for statistical significance between factors like age, gender, family history and need for psychology support.
Methods
It is a prospective study. A voluntary questionnaire was designed which had mixture of closed, open and multiple choice questions. Those children who attended paediatric outpatient diabetic clinic from March to May 2009 were included.

Results
Forty-eight children and families participated in the study. Of them, 52% ($n=25$) were male. The median age was 12 years (age range 2–16 years). 83% ($n=40$) of children asked for support in primary and secondary care, out of which 55% ($n=22$) asked for psychology support.

	Psychology support % (number)	No psychology support % (number)	*P* value (Fisher test)
Age under 10 years ($n=19$)	68% (13)	32% (6)	0.01
Male ($n=25$)	56% (14)	44% (11)	0.16
Family history of diabetes ($n=23$)	57% (13)	43% (10)	0.24

Conclusion
Requests for psychology support were highest in younger children (<10 years) and their families. Psychologists should be involved along with dietician, nurse and doctors when children are first diagnosed with diabetes. Mental health issues in childhood are likely to persist into early adulthood and appear to be prognostic of maladaptive lifestyle practices, and earlier-than-expected onset of complications.

P67

Clinic appointment reminders and their effect on 'did not attend' (DNA) rates and HbA1C, in a paediatric diabetes clinic

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Background
Non-attendance in outpatient clinics results in administrative problems, economic loss and poor patient care. Mobile phone intervention has been shown to be effective in improving attendance rates in chronic disease follow up. A pilot study conducted over 9 months in our diabetes clinic showed improved attendance following phone calls and text messages sent to carers/young people prior to their clinic appointment (statistical significance reached when patient spoken to, $P<0.05$).
Aims
(1) To analyse DNA rates when carers/patients were telephoned or texted prior to their clinic appointment over a 2-year period.
(2) Did the change in attendance result in improved HBA1c's?
Methods
Prospective 2 year study with the 1st 8 months serving as control (routine hospital appointments made by patient) followed by an 8-month period of calling carers/patients to remind them of their appointment and the third period of 8 months of text messaging reminders. Paired *t*-testing was used to compare DNA rates in the control and intervention period. The overall control of the clinic as reflected by average HBA1c and HBA1c at end of each period (control/phone/text messaging) was also compared.
Results
Data for 104 patients available. The proportion of clinics not attended decreased over the time period, though not statistically significant. ($P<0.45$). HbA1c and average HbA1c increased over the study period.
Conclusion
Our preliminary results do not support the findings of other studies which show a significant improvement in attendance following use of telephone or text message reminders, though notably, most of these have been over shorter periods of time. Sub analysis within our telephone and text messaging subsets is underway and may reveal better ways of improving clinic attendance. This study clearly identifies the need for scarce NHS resources to be directed appropriately at measures that are sustainable over longer periods and translate into improved patient outcomes.

P68

Survey of management of diabetes in schools

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Introduction
Type 1 diabetes mellitus is the third commonest chronic condition of childhood and unfortunately UK has one of the lowest percentages of children attaining good diabetes control in Europe. Department of Health has outlined recommendations to improve management of diabetes in schools and provide children with the necessary support required to achieve their maximum potential.
Objective
To evaluate the provisions available in Shropshire and Powys maintained schools for the management of children with diabetes.
Method
A postal questionnaire and covering letter, addressed to the head teachers of 83 schools identified as having at least one pupil with diabetes on their register was sent. 47 (57%) of these schools participated in the survey. Simultaneously parent satisfaction questionnaires were distributed to parents of children with diabetes attending specialist diabetes clinics at the hospital, which garnered 43 responses.
Results
17% of schools in Shropshire and Powys had a written diabetes policy. 79% of schools used personalised diabetes management plan and only 49% of the schools had a staff lead for diabetes. Written guidelines for management of hypoglycaemia were available in 60% of schools and 83% had facilities for safe storage of sharps. Parent satisfaction questionnaires revealed that 23% of parents felt that their child missed out on school activities due to diabetes. 65% of them felt that their child's hypoglycaemia was managed adequately in school and there was a wide variability in the degree of satisfaction of parents with their child's diabetes management in school.
Conclusion
Not every child with diabetes had a personalised diabetes management plan as against the Department of Health recommendations. Schools lacked adequate written guidance for the management of hypoglycaemia and there was need to provide more information and training opportunities to both school staff and school nurses in the management of diabetes in children.

P69

Experiences and attitudes towards clinics among pre-transitional and transitional adolescents with type 1 diabetes, a clinical attitudes survey

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Introduction
Adolescents with type 1 diabetes often have poor control causing them significant future danger. An area of particular concern is that of worsening control around the complex time of transition to young adult services from paediatric services. Multiple guidelines and methods to help better this control and transition process are in place.
Aim
This study aims to survey attitudes towards and possible improvements to clinics to aid adherence and attendance; to review whether guidelines on diabetic clinics and transition are being met; and to retrospectively analyse transition.
Methods
Anonymised questionnaires completed with adolescents at paediatric clinics across three different hospitals in Manchester. Questionnaires sent out to young adult cohorts from two different hospitals in Manchester.
Results
With a total population number of 50 in the paediatric cohort and 28 in the young adult cohort, results show that clinics are reaching national guidelines. However, the majority of teenagers are trying to hide their lack of control, and it is felt that broader support is needed to combat this in multiple forms such as texts between clinics, forms before clinics, mentors, social events, and group learning. Teenagers who have had diabetes for a shorter amount of time are statistically significantly more likely to want these methods of increased support. Centres are not meeting the NICE guidelines for transition, and young adults feel that they are met too few times before transition by the adult team.
Conclusion
Both treatment and methods of transitioning need to adapt to adolescents rather than expecting them to react to it. More support may be useful in controlling glycaemic levels, and pilots of these different methods should be trialled. The age at transition is not always correct; there is room for implementing different methods of deciding age of transition. Stricter guidelines should exist to make the transition process more sequential.

P70

Evaluation of the Lothian Diabetes Service for adolescents with type I diabetes mellitus

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Introduction
We evaluated the Lothian Adolescent Diabetes Service (LADS) to assess the service at the introduction of a clinical psychologist, to help guide service redevelopment and evaluate areas where psychological support would be most beneficial.
Methods
Over 13 weeks, all adolescents with type 1 diabetes mellitus attending LADS clinics were invited to complete a questionnaire about their clinic experience and support with diabetes management. Consent was requested to use data from their medical records, including HbA1C to allow evaluation of glycaemic control. Clinic attendance statistics over the study and preceding year were also recorded.
Results
72% of adolescents had a good/very good clinic experience and clinic attendance over 1 year was high (83.3%). However, 76% spent $\geq$1 h at clinic whilst 78% spent $\geq$50% of their visit waiting. The majority ranked the doctor as most important person to consult at clinic and dietician the least. 47.6% receive a lot of help with diabetes management but 77% want no change in responsibility. Mood was the topic most frequently requested for additional information and support. Only 10.7% of the adolescents had a mean HbA1C $<$7.5% (target HbA1C) over 1 year. Worryingly, a third of adolescents with HbA1C $>$9.0% perceived their glycaemic control as moderate to very good.
Conclusions
LADS provides a satisfactory service and support for adolescents. However, glycaemic control is suboptimal, which adolescents may not realise; increasing awareness should be prioritised. Recommended foci for service-wide development include reducing total and waiting clinic durations and development of dietician/psychologist roles.

P71

Type 2 diabetes in young adults in East London: an alarming increase

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Aims
Type 2 diabetes (T2DM) now affects a significant proportion of young people worldwide. 'X-borough' contains a strikingly young, diverse population with one of the highest rates of prevalence for adult T2DM in the UK. Our aims were to determine the prevalence and examine the characteristics of young people with T2DM in this population.
Methods
Forty-four young people ($<$25 years) with T2DM were matched with an equal number of young people with type 1 diabetes (T1DM). A retrospective study, utilising diabetes and pathology databases, was conducted.
Results
*Young people with T2DM were mostly female, of non-Caucasian descent (88%: $n=41$) and typically reported a positive family history of T2DM (97%: $n=30$). The average age at diagnosis was 15.2 years ($n=36$) and 25% were diagnosed incidentally ($n=16$). Average BMI was 33 kg/m^2 ($n=39$). Hypertension was diagnosed in 23% ($n=40$) and polycystic ovary syndrome (PCOS) in 22% of all females. Average HbA1c was 8.3% ($n=42$) and 27% had abnormal liver function ($n=41$). The prevalence of T2DM was calculated as 1.33/1000. In contrast, a higher proportion of young people with T1DM were of Caucasian descent. HbA1c was generally higher whilst average BP and BMI values were lower. A smaller number had abnormal liver function, hypertension and PCOS. Clinic non-attendances and hospital admissions were also lower for this group.
Conclusion
This study confirms the growing rise of T2DM with obesity in young people, particularly amongst ethnic minority groups and adds to concern among healthcare providers and commissioners about the need for preventative strategies to tackle this problem.

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Which test to use for screening glucose intolerance in overweight/obese children?

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Background
With the increasing prevalence of obesity and related morbidity including glucose intolerance in childhood, there remains a dispute about the best screening test to identify this early. The aim of our study was to determine the prevalence of impaired glucose tolerance (IGT)/type 2 diabetes mellitus (T2DM) in a multiethnic cohort of 100 overweight/obese children and adolescents in our clinic and compare the results of the screening tests.
Study
Over a 4-year period from 2006 to 2010, 100 overweight/obese children (UK 1990 BMI reference curves used) underwent screening for glucose intolerance using standardised WHO oral glucose tolerance test (OGTT), fasting insulin and HbA1c. Insulin resistance (IR) was defined using HOMA-IR index ($>$3 as cut-off).
Results
92% were obese and 8% overweight. 43% were of South Asian (SA) ethnicity, 55% White Caucasian (WC) and 2% other. 61% were females. Mean age was 12.9 years (range 2.5–18.1 years). Nine had IGT and one T2DM (SA) with the remaining 90% having normal OGTT. The prevalence of IGT was higher within SA group (14% in SA vs 5% in WC). All the children with IGT/T2DM had significantly higher HOMA-IR compared to normal OGTT (median: 8.21 (3.6–17.8) v 4.5 (0.5–22.2) but only 5/10 had HbA1c $>$ 6%. Of the 90 with normal OGTT ($n=4$ with no insulin data), 55/86 (64%) had evidence of IR -median HOMA-IR 6.2 (3–22.2) with 10/55 also having HbA1c $>$ 6%. Of the 31/86 (36%) with normal OGTT and no IR (median HOMA-IR 2.0 (0.5–2.9)), only 1 had HbA1c $>$ 6%. Only 5/100 had all three tests positive.
Conclusion
The prevalence of IGT/T2DM in multiethnic obese/overweight children is high and similar to previously reported studies. 65% of the screened population showed evidence of significant IR. The combination of OGTT with fasting insulin was found to be the best screening test.

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Syndromic obesity

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Aims
Childhood obesity is reaching epidemic proportions. Obesity may be primary (obesogenic environment), secondary (hormonal imbalance, drugs), monogenic (POMC) or be part of a complex phenotype-genetic obesity syndromes. It is important to distinguish between classifications. Our aim was to review our cohort of 'obese' patients with this in mind.
Methods
Patients referred to our Paediatric Endocrinology Service specifically for management of obesity and who ultimately and unexpectedly turned out to have a syndromic cause were identified from our database. Their case notes were reviewed. Detailed histories and physical examination findings are reported. Parental consent was requested and clinical photographs obtained in all cases. A review of paediatric, endocrinology and genetics literature was conducted in order to develop guidelines for recognising and investigating children with potential genetic obesity syndromes.
Results
We elucidated an underlying genetic pathology in six patients referred to our tertiary paediatric endocrinology service over a 2 year period from primary and secondary care for management of 'simple' or 'exogenous obesity'. We recommend targeted genetic testing $\pm$ liason with a clinical geneticist in patients with obesity in addition to learning difficulties, visual/hearing/behavioural problems, dysmorphism/skeletal anomalies, marked short/tall stature/abnormal head size or epilepsy.
Conclusion
Most obesity in Irish children is exogenous in nature. However, it is important to recognise children who may have a genetic cause for their obesity. There are many genetic obesity syndromes, the most frequently encountered being Prader–Willi, Bardet–Biedl and Alstrom's syndromes. Management is generally

symptomatic and multidisplinary rather than specific. Appropriate genetic counselling should be provided.

P74

Age at onset of inappropriate weight gain in Prader–Willi syndrome; an opportunity for obesity prevention

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Background
Prader-Willi syndrome (PWS) results from loss of paternally imprinted gene(s) from the 15q 11-13 region and is characterised by weight faltering during early childhood due to hypotonia, followed by obesity due to onset of the hyperphagic phase.
Aim of study
To determine the presence of an age zone during which excessive weight gain is particularly likely, in order to target counselling and dietary input.
Method
Body mass index (BMI) was calculated for each data point in 40 patients with PWS (M=24, F=16) from a single centre seen over a 20-year period. Two researchers independently scrutinised the chart for each patient and to estimate or identify the age at which an inappropriate rise in BMI began.
Results
Seventy-six patients were identified of which 36 had insufficient data for analysis leaving 40 for study. No inappropriate increase in BMI trend occurred in 10 patients, median (range) age at last data point 5.3 (1.5–15.2) years. Age at BMI increase could not be ascertained in 9 patients, all of whom became obese (BMI SDS >2) by 3.2 (2–5) years. Of 21 patients in whom age at BMI increase could be estimated (8) or precisely identified (13) the median age at the time of increase was 2 (0.5–3.8) years with 18/21 patients showing onset of increase between 1 and 2 years of age.
Conclusion
The critical age of excessive BMI increase in most PWS subjects is between 1 and 2 years. Structured input from a multidisciplinary team should be intensified at 1 year of life to pre-empt this trend.

P75

Orlistat prescribing in children in Scotland

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Introduction
Most paediatric medicines have not undergone extensive clinical trials in children and as a necessity are frequently prescribed off-label, a practice which is recognised to be associated with an increased risk of adverse drug reactions (ADRs).
Aims
To assess the use of routinely acquired healthcare data to identify medication utilisation and specifically drug discontinuation, as a signal for possible ADR occurrence in children: using orlistat as an exemplar.
Methods
Prescribing data held within the Primary Care Clinical Informatics Unit (PCCIU) database was used to assess prescribing and discontinuation of orlistat in children aged 18 years and younger, for the period 2006–2009. This drug was selected because it is not licensed for paediatric use and is associated with a significant ADR profile in adults. Orlistat discontinuation was defined as a cessation of a prescription within: <1, 1–3, 4–6 and >6 months of the index prescription.
Results
- During the study period 82 children were newly prescribed orlistat; (6–18 years, 81.7% females).
- 67% had a weight recorded prior to treatment, BMI SDS (0.54 to 5.4, mean 3.13).
- 53.7% of children discontinued orlistat within one month of the index prescription, and 74.4% within 3 months.

Using routinely collected healthcare data permitted the identification of children prescribed orlistat, the discontinuation rate, assessment of age, gender, BMI, SIMD score and adherence to treatment guidelines.
Conclusion
Our preliminary data confirms that routinely collected primary care healthcare datasets can be effectively used to assess medication prescribing profile and drug discontinuation in children. The 1 month discontinuation of 54% observed in this study is approximately double that reported for adults, but within the reported paediatric ADR prevalence of 30–100%, supporting the use of medication discontinuation as a potential signal for ADRs.

P76

Impact of community based weight management programmes on hospital based dietetic activity

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The management of childhood obesity has evolved from hospital led treatment to community-based programmes. This is an audit reviewing the impact of the active children eating smart (ACES) programme for overweight/obese children on the dietetic department in the Royal Hospital for Sick Children; Glasgow. A retrospective audit was carried out of referrals to the dietetic department. Clinic lists for dietetic appointments in 2008 and 2010 were identified and reviewed. In 2008 and 2010 2.7% (28) and 5.9% (70) of total dietetic referrals were for overweight/obesity. There was a decrease in the number of dietetic appointments allocated to childhood overweight/obesity in 2010 (1.8%) in comparison to 2008 (2.7%). The decrease in appointments allocated to overweight/obesity is due to the ability of dieticians to re-refer patients to the ACES programme. Being able to refer to the ACES programme has led to a reduction in attrition rates, as there is poor clinic attendance for children referred with increased weight. Proportionally children under 5 years account for more appointments for overweight/obesity in 2010 than in 2008. There are a higher proportion of boys referred to the dietetic department with overweight/obesity than girls. The majority of children referred to the dietetic services for overweight/obesity are from the most deprived areas in the Greater Glasgow area. Referrals that were deemed more suitable to be referred to ACES were considered inappropriate referrals. The majority of the inappropriate referrals originated within the hospital; RHSC, 40.4%. Inappropriate referrals from community health centres, GP and the health visitor accounted for 38.3%, 19.2% of the referrals and 2.1% respectively. The ACES programme has impacted on the number of referrals to the dietetic department. Health care professionals would benefit from further education on the management options available for childhood obesity, including further information on the ACES programme.

P77

Octreotide treatment for congenital hyperinsulinism can cause hepatitis

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Introduction
Congenital hyperinsulinism (CHI) is a rare condition of dysregulated insulin secretion causing hypoglycaemia. Oral Diazoxide is used as first line therapy for CHI. In those who are Diazoxide unresponsive, subcutaneous Octreotide is used as second line treatment. Octreotide has recognised side effects of biliary stasis. Additionally, we report hepatitis as a complication of Octreotide therapy in a child with CHI.
Case report
A neonate with CHI with a compound heterozygous ABCC8 mutation was treated with Diazoxide. As glycaemic response was unsatisfactory, Octreotide was commenced with doses increasing to 20 μg/kg per day with suboptimal glycaemic stabilisation. Subsequently, the patient underwent subtotal pancreatectomy with the achievement of normoglycaemia for 3 months. Thereafter, further episodes of hypoglycaemia were noted. Octreotide was recommenced and doses were escalated to 40 μg/kg per day to achieve satisfactory glycaemic control. However, with high doses, a marked and persistent elevation in the liver enzyme alanine transaminase (ALT) (maximal value 1061 IU/l, normal level <50 IU/l) was noted. The presence of abnormal ALT was investigated by a hepatitis screen, which included viral titres, antibodies, imaging and liver biopsy, all of which were normal. The patient underwent a second pancreatectomy at age 2.8 years, following which glycaemic stabilisation was achieved and Octreotide was withdrawn. Two days after withdrawal of Octreotide, ALT levels returned to normal. The presence of elevated ALT after Octreotide administration and return to normal levels after withdrawal suggests a causal link between Octreotide and hepatitis.

Discussion
Treatment with Octreotide for children with Diazoxide-unresponsive CHI may be complicated by biliary side effects. We have now reported hepatitis as a complication of Octreotide, which has not been previously recognised. Our case highlights the importance of monitoring liver enzymes whilst on Octreotide therapy. In children with hepatitis due to Octreotide, medical treatment should be terminated and pancreatectomy considered early to achieve glycaemic stabilisation.

P78

Audit of Endocrine Adolescent Transition Clinic, RHSC Glasgow, 2008–2010

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Introduction
A multi-disciplinary endocrine Adolescent Transition Clinic (ATC), with key professionals from paediatric and adult services, was instituted at the Royal Hospital for Sick Children, Glasgow, in October 2008 serving young people in the West of Scotland. A good transition should improve clinic attendance, health outcomes and quality of life into adulthood.
Aim
To systematically review the success of ATC in engaging young people following their transfer to an adult endocrine service.
Methods
Three-monthly ATC lists were reviewed to identify patients who were no longer being reviewed in a paediatric setting. Confirmation of transfer was obtained by reviewing the last available ATC letter. A combination of a Glasgow-wide electronic patient record and telephone contact with medical secretaries was used to determine clinic attendance and DNA rates between final ATC and June 2011. Results are expressed as median (range).
Results
Fourteen young people (8 males), with median age at last ATC visit of 18.7 years (16.5, 23) were transferred to six adult endocrine services in the West of Scotland after 2 (1, 3) ATC attendances. The diagnoses (number of patients) included: panhypopituitarism (9) (acquired secondary to craniopharyngioma (4); cranial irradiation (2); infiltration in iron overload (2); and traumatic brain injury (1)); congenital adrenal hyperplasia (2); Klinefelter syndrome (1); congenital hypothyroidism (1) hypogonadotrophic hypogonadism (1). The frequency of adult endocrine clinic attendance was 4 (1, 5) clinics/year. The interval between last ATC to adult clinic was 0.45 (0.09, 1.14) yrs. All patients attended the first adult clinic appointment offered. The subsequent DNA rate was only 9% with no young person lost to follow-up. Of 14, 11 had complex care needs requiring input from more than one adult subspecialty team.
Conclusion
The endocrine ATC is successful in engaging young people in adult endocrine care. A dedicated young-adult endocrine clinic, in the adult hospital, may help retain young people in an adult clinic setting long-term. Coordination between specialist teams at transition may be required to provide a more seamless transfer of patient care.

P79

Clinical characterisation of hyperinsulinaemic hypoglycaemia associated with intra-uterine growth restriction

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Background
Intra-uterine growth restriction (IUGR) is a known risk factor for the development of hyperinsulinaemic hypoglycaemia (HH). The phenotype of a large cohort of neonates who develop HH following IUGR has not been studied previously.
Aim
To characterise the clinical aspects of a cohort of neonates with IUGR who developed HH.
Methodology
Thirty-nine patients with IUGR (defined as birth weight $<$10th centile) who presented in the neonatal period with biochemically confirmed HH and referred to a tertiary endocrine hospital were recruited. Detailed clinical information was collected, followed by sequencing of *KCNJ11* and *ABCC8* genes.
Results
All except one patient required initiation of diazoxide therapy. 37/38 responded to treatment with diazoxide (5–10 mg/kg per day) and chlorothiazide (7–10 mg/kg per day) to correct their hypoglycaemia. Each of these patients was followed up at 1–3 monthly intervals and diazoxide withdrawal was undertaken when clinically indicated. In 6 patients, diazoxide and chlorothiazide therapy was stopped within 3 months of age, in 16 further patients within 6 months and in 6 further patients within a year of birth. Five patients had HH requiring diazoxide support for >1 year of age (oldest continuing diazoxide support at 23 years of age). The outcome is not known in four patients.
In 35/37 patients tested, mutations in *ABCC8/KCNJ11* were not identified. Two patients were identified to have a paternally inherited *ABCC8* mutation, with one confirmed to have a focal lesion requiring pancreatectomy.
Conclusion
Infants with IUGR may continue to have hypofattyacidaemic hypoketotic HH beyond the first few weeks of life. Recognition and treatment of this group of patients is important and may have important implications for neurodevelopmental outcome of these patients. The genetic aetiology of HH in the vast majority of infants with IUGR is not understood. Further studies are needed to understand the underlying mechanism of these observations.

P80

Congenital hyperinsulinism: marked clinical heterogeneity in siblings with identical mutations in the *ABCC8* gene

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Congenital hyperinsulinism (CHI) is a clinically and genetically heterogeneous disease. The clinical heterogeneity may range from mild subtle hypoglycaemia to severe life threatening hypoglycaemia. The commonest genetic cause of congenital hyperinsulinism are mutations in the genes *ABCC8* and *KCNJ11* encoding the two subunits (SUR1 and Kir6.2 respectively) of the pancreatic β-cell K_{ATP} channel. In the Ashkenazi Jewish population two founder mutations in the *ABCC8* gene account for about 88% cases of CHI, with the splicing (c.3992-9G$>$A) mutation being the most prevalent. We report a family with marked intrafamilial clinical variation in four haploidentical siblings who have the same homozygous c.3992-9G$>$A mutation in the *ABCC8* gene. This clinical heterogeneity ranged from having no symptoms of hypoglycaemia to having macrosomia, transient hyperinsulinism to severe hyperinsulinism and then gradual improvement over time followed by development of diabetes mellitus. It is unclear how the same mutation causes such marked clinical heterogeneity. It is possible that the clinical expression may be modified by background genetic factors and other unknown factors involved in regulating gene expression.

P81

An audit of diazoxide prescriptions in children with congenital hyperinsulinism: preliminary recommendations

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Introduction
Congenital hyperinsulinism (CHI) is characterised by abnormally regulated and excessive insulin secretion by pancreatic β cells. First line management includes an oral suspension of Diazoxide but a standardised formulation is not universally employed. Anecdotal evidence suggests that different formulations can alter the management of glucose levels. Lack of glucose control can lead to permanent brain damage and adversely affect neuro development.
Aims
To assess i) the information given to general practitioners (GPs) and carers about the Diazoxide formulation, and ii) effects on home blood glucose levels observed with changes in the Diazoxide formulation.
Methods
The management of 33 CHI patients treated with Diazoxide suspension was evaluated by i) reviewing electronic GP letters or nurse's records and ii) a structured telephone interview with carers.
Results
Electronic GP letters and nurse's records were available for 29/33 patients. Of these, 14% (4/29) specified the Diazoxide formulation as Proglycem (Gates

Pharmaceuticals, USA). The specific Diazoxide formulation was not explicitly stated in the remaining. Telephone interviews with carers were conducted for 24/33 patients. Of these, 29% (7/24) children were on Proglycem and 96% (23/24) reported changes to the formulation when a repeat prescription was obtained from the GP. Among the latter, 48% (11/23) had variations in blood glucose control and hypoglycaemia in association with a change to Diazoxide formulations other than Proglycem.
Conclusion
Recurrence of hypoglycaemia was reported in almost half of the children with CHI when a formulation other than Proglycem was prescribed. Proglycem should be stated as the formulation of choice for Diazoxide suspension in all written communication to GPs and in the verbal information given to carers.

P82

(Pseudo)hyperkalaemia caused by stomatin deficient cryohydrocytosis due to GLUT1 deficiency

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Hereditary stomatocytoses, including cryohydrocytosis, are anaemias in which the erythrocyte membrane has increased permeability resulting in electrolyte leakage and thus haemolysis. Many forms and underlying molecular mechanisms exist. GLUT1 is present in the blood–brain barrier and erythrocytes, but GLUT1-deficiency does not usually affect erythrocytes. We describe a child with a stomatocytosis due to a *SLC2A1* mutation presenting with hyperkalaemia, liver disease, microcephaly, nystagmus, and seizures.
The patient presented aged 1 day with jaundice and hypoglycaemia, and was treated for presumed sepsis. Plasma K^+-concentration was reported to be >8 mmol/l. The child continued to have conjugated hyperbilirubinaemia; a liver biopsy suggested non-specific hepatitis. She developed abnormal movements, nystagmus and microcephaly; EEG was normal but MRI showed periventricular calcifications. Aged 4 months, she developed seizures and was developmentally delayed. Hyperkalaemia continued, requiring occasional treatment with Salbutamol, Insulin or Fludrocortisone. Adrenal pathology was excluded. Investigation suggested normokalaemia when samples were assayed immediately and therefore 'pseudo-hyperkalaemia'. Continuing hyperbilirubinaemia and occasional splenomegaly lead to a suspicion of a 'leaky erythrocytes'. Incubation of blood at 37, 20 and 0 °C, showed increasing extracellular K^+-concentration and decreasing intracellular K^+-concentration with reducing temperature, and deranged intracellular Na^+/ K^+-concentration in fresh erythrocytes, suggesting 'stomatin-deficient cryohydrocytosis'. Indeed, a blood film showed erythrocyte fragments. Glucose-concentration in CSF was 2.0 mmol/l (plasma 3.8 mmol/l), consistent with reduced glucose transport across the blood–brain barrier. Direct sequencing of *SLC2A1* revealed a *de novo* heterozygous ATC deletion (p.Ile435or436del). This *SLC2A1*-mutation has been found previously in an adult with stomatin-deficient cryohydrocytosis but this is the first paediatric presentation described. The mutation both prevents glucose transport and causes a cation leak. A ketogenic diet improved seizures and reduced abnormal movements, as in the more common GLUT1-deficiency syndrome. In conclusion, pseudohyperkalaemia needs to be considered in assessment of hyperkalaemia. GLUT1-deficient cryohydrocytosis may present with haemolytic anaemia, pseudohyperkalaemia and neuro-pathology.

P83

Galactokinase deficiency in a patient with congenital hyperinsulinism: the cautionary tale of using bedside blood glucose monitors

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Background
Galactokinase catalyses the first committed step in galactose metabolism, the conversion of galactose to galactose-1-phosphate. Galactokinase deficiency is an extremely rare form of galactosaemia and the most frequent complication reported is cataracts. Congenital hyperinsulinism (CHI) is a cause of severe hypoglycaemia in the newborn period.
Aims
To report the diagnostic pitfalls with bedside blood glucose testing in a neonate with combined galactokinase deficiency and severe congenital hyperinsulinism.
Patients/methods
A term baby girl from consanguineous parents presented with poor feeding, irritability and seizures. Capillary blood glucose testing using bedside test strips and glucometer showed a glucose level of 18 mmol/l but the actual laboratory blood glucose level (measured by glucose oxidase method) was only 1.8 mmol/l. Urine reducing substances were positive. Once oral feeding, the main dietary source of galactose, was stopped the test capillary blood glucose level correlated with the laboratory blood glucose level.
Results
Biochemically the patient had CHI (blood glucose 2.3 mmol/l with simultaneous insulin of 30 mU/l) and galactokinase deficiency (with elevated serum galactose level of 0.62 μmol/h per g Hb). The CHI failed to respond to medical treatment and required a near total pancreatectomy. Homozygous mutations in ABCC8 (E128K (c.382G>A; p.Glu128Lys) in exon 3) gene and GALK1 (homozygous R256W (c.766C>T; p.Arg256Trp) missense mutation in exon 5) lead to CHI and galactokinase deficiency respectively.
Conclusion
This is the first reported case of CHI and galactokinase occurring in the same patient. Severe hypoglycaemia in neonates with CHI may go undetected with bedside blood glucose meters in the presence of galactokinase deficiency.

P84

Mevalonic aciduria in a pedigree with presumed GH-insensitivity

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Mutations in *GHR*, *STAT5B* and *IGF1* lead to GH-insensitivity but often the cause of reduced GH-sensitivity remains unknown. We describe the identification of a mutation in the *MVK* gene encoding mevalonate kinase (MK) in a pedigree investigated for STAT5B-deficiency.
A 15-year-old male born to consanguineous parents was referred for short stature (height 125.8 cm; −5.6 SDS) and arthritis. He presented, aged 2 years, with fever and poly-arthritis, and continued to have episodes of fever, hepatosplenomegaly and gastritis/duodenitis, and developed cataracts. A liver biopsy showed sclerosing cholangitis. He was on steroid treatment for presumed auto-immune disease. Pubertal development was delayed. The peak GH in response to provocation was 6 μg/l. Plasma IGF1-concentration was 27 μg/l (140–887) and IGFBP3 1.05 mg/l (3–8 mg/l). GH-treatment (6–10 mg/m^2 per week) had little effect on growth and IGF1-concentration. One affected sister died of peritonitis. Two sisters had short stature, poly-arthritis and delayed puberty; one received GH-treatment with little effect. Six siblings were unaffected.
Microsatellite analysis and homozygosity screening of three affected and four unaffected family members pointed to a region on chromosome 12q24, not containing *STAT5B*. Candidate gene sequencing excluded *SOCS2* mutations and detected a novel homozygous missense mutation (p.Val310Leu) in *MVK* in all three affected siblings, affecting a highly conserved valine; a previously described p.Val310Met mutation resulted in severe MK-deficiency. The mother and two unaffected siblings were heterozygous. The third unaffected sibling and 100 controls did not carry the mutation. MK is the enzyme following HMG-CoA in isoprenoid and cholesterol biosynthesis, important for several cellular processes. MK-deficiency leads to mevalonic aciduria, characterised by short stature, developmental delay, hepatosplenomegaly, arthritis, cataract and periodic inflammation, or the milder hyperimmunoglobulinaemia D. In conclusion, mevalonic aciduria was revealed in a pedigree with presumed GH-insensitivity. Growth failure is likely due to a combination of liver dysfunction, inflammation, steroid treatment and possibly MK-deficiency directly.

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